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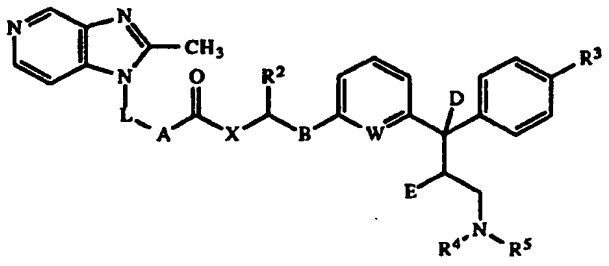

(II)

(57) Abstract

Compounds of formula (II), wherein L, A, X, B, R^2, R^3, W, D, E, R^3, R^4, R^5 are as defined in the specification, are dual histamine H1 and PAF receptor antagonists.

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Imidazopyridine Derivatives

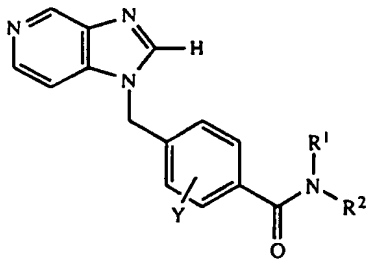
This invention relates to compounds which are dual histamine (H_1) and platelet activating factor (PAF) receptor antagonists, to therapeutic compositions containing such compounds, and to methods for their preparation.

Background to the Invention

Potent H_1 receptor antagonists of various structural types are known, and are useful in treating the symptoms of inflammatory conditions such as allergic rhinitis, and allergic conditions of the skin, which are mediated at least in part by the release of histamine. However, in such conditions, in which histamine release plays a causative role; there may be other mechanisms at work which are not inhibited by treatment with an H_1 receptor antagonist alone. For example PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a wide variety of physiological responses, including hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, increased vascular permeability (oedema/erythema), and accumulation of inflammatory cells in the lower airways.

There is therefore a need for agents which have dual H_1 and PAF receptor antagonistic activity for the improved treatment of conditions mediated by histamine and PAF release. Such conditions include allergic rhinitis, sinusitis, asthma, dermatitis, psoriasis, urticaria, anaphylactic shock, conjunctivitis, pruritis, inflammatory bowel disease and colitis.

European patent specification EP-B-404797 (G.D. Searle) claims a series of PAF receptor antagonists of general formula (I)



(I)

wherein Y, R^1 and R^2 are as defined in the publication itself.

International patent applications WO-A-92/03423 (British Biotechnology) and WO-A- 9516687 and United States patent US5180724 (British Biotechnology) disclose series of compounds, incorporating a 2-methylimidazo[4,5-c]pyridine group which are potent antagonists of the PAF receptor.

United States patent US2712020 (Burroughs Wellcome) and European patent applications EP-A-085959 and EP-A-133534 (Wellcome Foundation) disclose compounds which are potent H_1 receptor antagonists.

International patent applications WO-A-92/14734 (Pfizer), WO-A-92/00293 (Schering), WO-A-89/10363 (Schering), WO-A-93/20080 (Schering), WO-93/20063 (Schering), WO-A-93/23400 (Schering), WO-A-93/02081 (Schering), WO-A-94/08581 (Toray), European patent applications EP-A-515158 (Schering), EP-A-463873 (Sankyo), EP-A-549364 (Sankyo), EP-A-577957 (Uriach) and Japanese patent application published under no 4-226993 (Yoshitomi) all disclose compounds which possess both histamine (H_1) and PAF receptor antagonist activity.

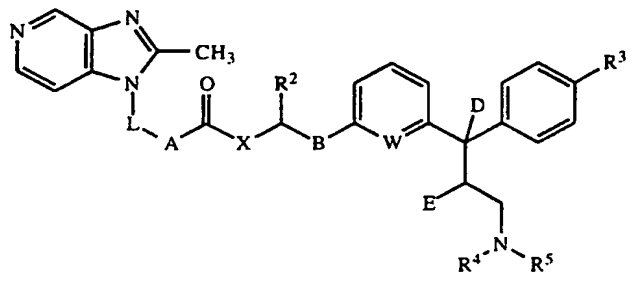
Brief Description of the Invention

The invention makes available a class of compounds with some of the structural features of the potent PAF receptor antagonists of WO-A-92/03423 and

US5180724, and structural features of H_1 receptor antagonists of for example US2712020, united in a single molecule in such a way as to provide a desirable balance of H_1 and PAF receptor antagonist activity. Furthermore, it has been shown that, in such compounds the structural features of the histamine fragment are also important for providing high affinity for the PAF receptor.

Detailed Description of the Invention

According to the present invention there is provided a compound of formula (II)



(II)

wherein:

L and A are such that (i) L represents an unbranched saturated or unsaturated divalent hydrocarbon chain having up to 6 carbon atoms and A represents a bond, or (ii) L represents a bond or $-CH_2-$ and A represents a divalent 1,4-phenylene group which may be substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, cyano, halogen or C_1-C_6 alkoxy;

X represents (a) -O-; or (b) $-N(R^1)-$ wherein R^1 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl or non-aromatic 5 to 7

membered heterocyclyl, any of which which may be substituted with one or more C_1-C_6 alkyl, -(C=O)O(C_1-C_6 alkyl), -COOH, or phenyl groups;

R^2 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl or non-aromatic 5 to 7 membered heterocyclyl which may be substituted with one or more C_1-C_6 alkyl, -(C=O)O(C_1-C_6 alkyl), -COOH, or phenyl groups;

B represents a bond, or a straight or branched saturated or unsaturated divalent hydrocarbon chain of up to 3 carbon atoms;

R^3 represents hydrogen, C_1-C_4 alkyl, halogen, cyano, trifluoromethyl or C_1-C_4 alkoxy;

W represents -N= or -C=;

D represents hydrogen or a hydroxyl and E represents hydrogen, or D and E taken together represent -C=C-;

R^4 and R^5 are independently C_1-C_6 alkyl or together with the nitrogen atom to which they are attached form a non-aromatic 5-7 membered heterocyclic ring, which may contain one or more heteroatoms other than the nitrogen to which R^3 and R^4 are attached;

or a pharmaceutically or veterinarily acceptable acid addition salt, solvate or hydrate thereof.

Hereafter in this specification the term "compound" includes "salt", "solvate", or "hydrate" unless the context requires otherwise.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C_1-C_6 alkyl" or "saturated hydrocarbon chain having up to 6 carbon atoms" refers to a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl. A divalent saturated hydrocarbon chain having up to 6 carbon atoms is such an alkyl moiety having two unsatisfied valencies, including, for example, 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,5-pentylene, and 1,6-hexylene.

The term "C_2-C_6 alkenyl" refers to a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms and having in addition one double bond of either cis or trans stereochemistry where applicable. This term would include, for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

The term "unsaturated hydrocarbon chain of up to 6 carbon atoms" refers to a straight or branched chain C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety , and a divalent unsaturated hydrocarbon chain having up to 6 carbon atoms is a C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety having two unsatisfied valencies, including, for example, 1,2-ethenylene, 1,3-prop-1-enylene, 1,3-prop-2-enylene, 1,2-ethynylene, 1,3-prop-1-ynylene, 1,3-prop-2-ynylene,

As used herein, the term "C_3-C_8 cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "non-aromatic 5 to 7 membered heterocyclyl" refers to a

non-aromatic monocyclic heterocyclic group having from 5 to 7 ring atoms wherein the heteroatom(s) are selected from O, S and N. Illustrative of such are morpholinyl, thiomorpholinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, piperidinyl, pyrrolidinyl, pyrrolinyl, dioxolanyl, oxathiolanyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, pyranyl, dioxanyl, dithianyl, oxathianyl, and piperazinyl.

As used herein, the term "divalent phenylene" group means a benzene ring in which two of the ring carbons have unsatisfied valencies.

Compounds of this invention may contain one or more asymmetric carbon atoms, giving rise to either a pair of enantiomers (in the case of one asymmetric carbon atom), or to diastereoisomers, each of which consists of two enantiomers (in the case of more than one asymmetric carbon atom), with the appropriate R or S stereochemistry at each chiral centre. The invention includes all such enantiomers and diastereoisomers, and mixtures thereof.

The term "pharmaceutically or veterinarily acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human or animal consumption.

Examples of pharmaceutically and/or veterinarily acceptable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate, citrate, mesylate, benzoate, tosylate and tartrate salts.

Compounds of formula (II) include those in which, independently or in any compatible combination:

L and A are such that (i) L represents a C_1-C_6 alkylene group and A represents a bond, or (ii) L represents a bond or -CH_2- and A represents a divalent 1,4-phenylene group which may be substituted by C_1-C_6 alkyl, halogen or C_1-C_6 alkoxy. An example of case (i) is where L is 1,2-ethylene or

1,3-propylene and A is a bond. Examples of case (ii) include those where L is a bond or, preferably, $-CH_2-$, and A is 1,4-phenylene, 3-fluoro-1,4-phenylene or 3-methoxy-1,4-phenylene.

X represents (a) -O-; or (b) $-N(R^1)-$ wherein R^1 represents hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, 3,5-dimethylcyclohex-1-yl, methyl, ethyl, 3-methylbut-1-yl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-propyl, isopropyl, n-pentyl, n-nonyl, 2-ethylcarboxylate-3-methylbut-1-yl, benzyl, or tetrahydropyranyl. Preferably X is $-N(R^1)-$ where R^1 is cyclohexyl, methyl or ethyl.

R^2 represents hydrogen or C_1-C_6 alkyl, eg methyl. Preferably R^2 is hydrogen.

B represents a straight saturated or mono-unsaturated divalent hydrocarbon chain having 2 or 3 carbon atoms eg $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-, $-CH_2CH=CH-$, or $-CH=CHCH_2-$. In the case where B is a straight chain C_2 or C_3 divalent alkenyl group, the double bond preferrably has the trans stereoconfiguration. Preferred is -CH=CH- (trans).

R^3 represents hydrogen, C_1-C_4 alkyl eg methyl, or halogen eg chloro. Preferred is methyl.

W represents -N=;

D and E taken together represent -C=C-;

R^4 and R^5 are independently C_1-C_6 alkyl or together represent a group $-(CH_2)_m-$ wherein m is 5, 6 or, preferably, 4;

A compound of the present invention which is presently particularly preferred for its combination of PAF and H_1 receptor antagonistic activity and its activity following oral administration is N-cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

and its salts hydrates and solvates.

Another preferred compound of the invention is N-ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide, and its salts hydrates and solvates.

Additional specific compounds of the invention are:

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]prop-2E-enyl ester,

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]propyl ester,

N-Methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-(3-Methyl-but-1-yl)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-*iso*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Cyclopentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-(R,S) *sec*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-*tert*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-3,5-Dimethylcyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-*iso*-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

(S)-4-Methyl-2-([4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-benzoyl]-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-amino)-pentanoic acid ethyl ester,

N-Benzyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-propyl}-benzamide,

N-Cyclopropyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

(R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]but-3E-en-2-yl ester,

N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-p-chlorophenyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-4-Tetrahydropyranyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Pentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Nonyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Hexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

(R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid (E)-1-[6-(3-

pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]hex-1E-en-3-yl ester,

N-Ethyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propylamide,

N-Cyclohexyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butylamide

N-Cyclohexyl-3-fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

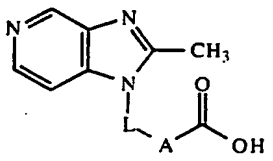
N-Cyclohexyl-3-methoxy-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

and their salts, hydrates and solvates.

Compounds of the invention of general formula (II) may be prepared by standard techniques of organic synthesis.

Route 1

Compounds of the invention in which X represents -O- may be prepared by esterification of an acid of formula (III) with an alcohol of formula (IV);



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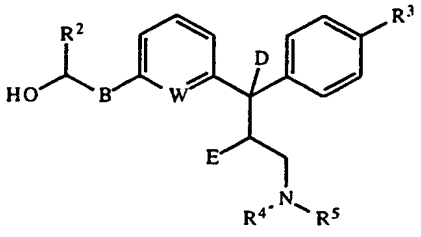
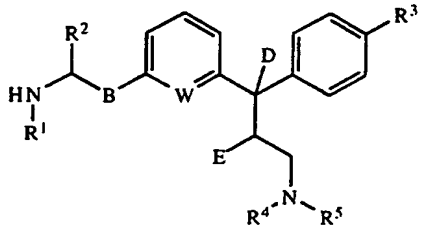


(IV)

wherein L, A, R^2, B, W, D, E, R^3, R^4 and R^5 are as defined in formula (II). The esterification may be performed in the presence of a carbodiimide condensing agent such as (N)-3-dimethylaminopropyl-N'-ethyl-carbodiimide. Alternatively, an activated derivative of the acid (III) may be employed for the esterification, such as the acid chloride or pentafluorophenyl ester.

Route 2

Compounds of the invention in which X represents -N(R^1)- may be prepared by amidation of an acid of formula (III) with an amine of formula (V);

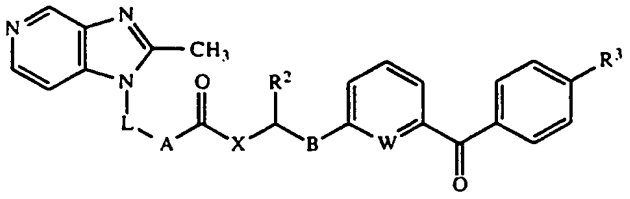


(V)

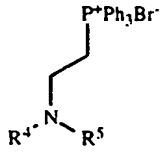
wherein R^1, R^2, B, W, D, E, R^3, R^4 and R^5 are as defined in formula (II). The amidation may be performed in the presence of a carbodiimide condensing agent such as (N)-3-dimethylaminopropyl-N'-ethyl-carbodiimide or using an activated derivative of the acid (III) as for the esterification. The reaction may be facilitated by the addition of for example 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole.

Route 3

Compounds of the invention in which D and E taken together represent -C=C- may be prepared by the reaction between a ketone of formula (VI) and a Wittig reagent formed by the treatment of a phosphonium salt of formula (VII) with a strong base such as n-butyllithium;



(VI)

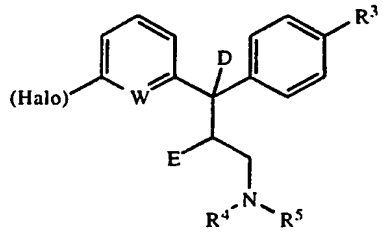


(VII)

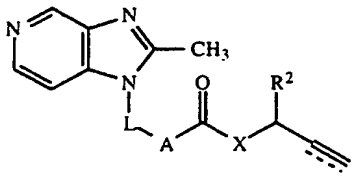
wherein L, A, R^2, B, X, W, R^3, R^4 and R^5 are as defined in formula (II). This reaction may be performed in the presence of a suitable solvent such as toluene.

Route 4

Compounds of the invention in which B represents an alkenyl or alkynyl group may be prepared by the palladium catalysed cross coupling reaction between a halide of formula (VIII) and an unsaturated compound of formula (IX);



(VIII)

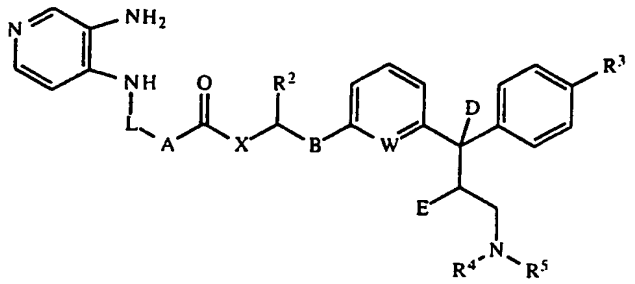


(IX)

wherein L, A, R^2, X, W, D, E, R^3, R^4 and R^5 are as defined in formula (II) and "halo" is prefferably iodo or bromo. Preferred catalysts are palladium(II) catalysts such as $Pd(OAc)_2$, $Pd(OAc)_2/PPh_3$ etc. The coupling reaction may be carried out in a suitable solvent such as DMF or dimethoxyethane and at elevated temperatures of about 80-160°C.

Route 5

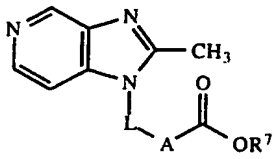
Compounds of the invention of formula (II) may also be prepared by a process comprising reaction of a diamino compound of formula (X), with acetic acid or a derivative thereof;



(X)

wherein L, A, X, R^2, B, W, D, E, R^3, R^4 and R^5 are as described in formula (II). This reaction is analogous to that described previously in WO-A-92/03423.

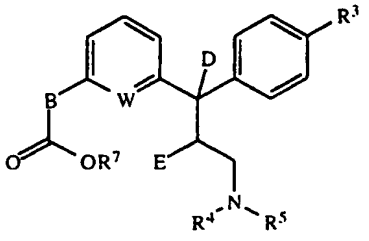
The starting carboxylic acids of formula (III) may be prepared by either acid or base hydrolysis of the corresponding esters of formula (XI) to provide an acid or base salt respectively;



(XI)

wherein L and A are as defined in formula (II) and R^7 is C_1-C_6 alkyl or benzyl. Esters of formula (XI) may be prepared as described in the literature eg WO-A-93/16075 (British Biotechnology), WO-A-90/11280 (Pfizer) and WO-A-92/14734 (Pfizer).

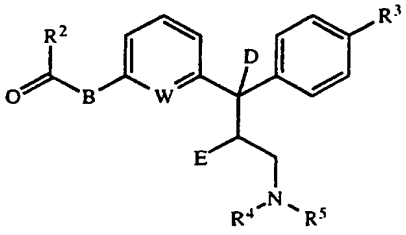
The alcohols of formula (IV) may be prepared by the reduction of esters of formula (XII) in the presence of a reducing agent such as diisobutylaluminium hydride;



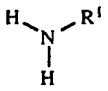
(XII)

wherein B, W, D, E, R^3, R^4 and R^5 are as defined in formula (II) and R^7 is as defined for formula (XI). Esters of formula (XII) may be prepared using routes analogous to those described in the literature eg EP-085959-A2 (Wellcome).

The amines of formula (V) may be prepared by the oxidation of alcohols of formula (IV) to aldehydes or ketones of formula (XIII) with an oxidizing agent, such as manganese dioxide, followed by reductive amination with an amine of formula (XIV);



(XIII)



(XIV)

wherein R^1, R^2, B, W, D, E, R^3, R^4 and R^5 are as defined for formula (II). The reductive amination may be facilitated by a reducing agent such as sodium borohydride in a suitable solvent, such as methanol or in the presence of a palladium catalyst under an atmosphere of hydrogen.

As mentioned above, the invention makes available a class of compounds having a desirable balance of H_1 and PAF antagonist activity.

Accordingly in another aspect, this invention concerns:

(i) a method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound as defined with respect to formula (II) above, or a pharmaceutically acceptable salt thereof; and

(ii) a compound as defined with respect to formula (II) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF; and

(iii) the use of a compound as defined with respect to formula (II) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF.

Diseases or conditions mediated by histamine and/or PAF, but which probably include contributions from both agents, include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, increased vascular permeability (oedema/erythema), allergic rhinitis, sinusitis, asthma, dermatitis, psoriasis, urticaria, anaphylactic shock, conjunctivitis, pruritis, inflammatory bowel disease and colitis.

According to a further aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula (II) and a pharmaceutically and/or veterinarily acceptable carrier. One or more compounds of general formula (II) may be present in association with one or more non-toxic pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula (II) may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol

monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical application to the skin compounds of the invention may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, compounds of the invention may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or

chlorohexidine, and thickening agents such as hypromellose may also be included.

Compounds of the invention may be administered parenterally in a sterile medium. The drug depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of the invention may be used for the treatment of the respiratory tract by nasal or buccal administration of, for example, aerosols or sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 1.0 mg to about 3.5 g per patient per day). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 0.1 to 10 mg of the drug.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral

administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

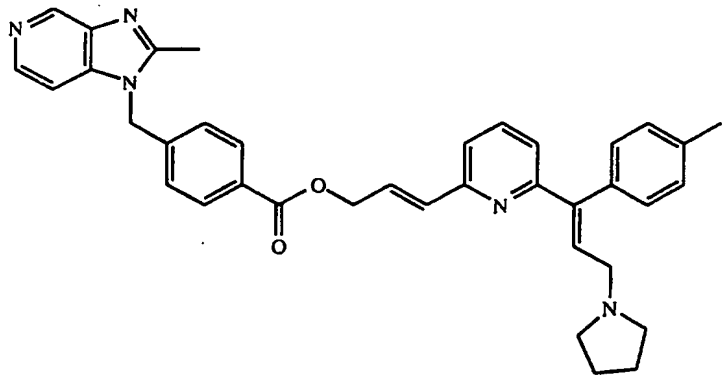
The following examples illustrate the invention, but are not intended to limit the scope in any way. The following abbreviations have been used in the examples:-

DCM - Dichloromethane
DMF - Dimethylformamide
HOAt - 1-Hydroxy-7-azabenzotriazole
DIBAL - Diisobutylaluminium hydride
EDC - N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
DMAP - N,N-Dimethylaminopyridine
HCl - Hydrochloric acid

Anhydrous magnesium sulphate and sodium sulphate were used as drying agents. Column chromatography was performed with flash grade silica gel. ^{1}H-NMR and ^{13}C-NMR were recorded either on a Bruker AC-250 spectrometer at 250 MHz and 62.5 MHz respectively or on a Bruker AMX-500 spectrometer at 500MHz and 125.72 MHz respectively. $CDCl_3$ or d_4-methanol (MeOD) were used as a solvent and internal reference and spectra are reported as δ ppm from TMS.

Example 1

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]prop-2E-enyl ester.



(a) Methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylate.

A solution of (E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylic acid (2.04g, 5.9mmol) in methanol (50ml) was treated with concentrated HCl (10ml) and stirred at room temperature for 6 days. The reaction was neutralised with a saturated solution of sodium hydrogen carbonate and solvent removed under reduced pressure. DCM was added to the residue and inorganic solids removed by filtration. Concentration of the filtrate under reduced pressure yielded methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylate as a pink foam (1.98g, 93%). ^{1}H-NMR; δ ($CDCl_3$), 7.70 (1H, d, J=15.7Hz), 7.57 (1H, t, J=7.7Hz), 7.30 (1H, t, J=7.6Hz), 7.25 (2H, d, J=8.3Hz), 7.17 (1H, d, J=7.2Hz), 7.10 (2H, dt, J=8.2, 1.8Hz), 6.96 (1H, d, J=15.6Hz), 6.93 (1H, d, J=7.9Hz), 3.83 (3H, s), 3.65 (2H, bs), 2.85 (4H, bm), 2.41 (3H, s) and 2.04 (4H, bm).

(b) 3-(6-[3-Pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-ol.

A solution of methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)acrylate (1.98g, 5.47mmol) in dry THF (100ml) was cooled to -78°C and treated under an inert atmosphere with a solution of DIBAL (1M in toluene, 16.4ml, 16.4mmol). After stirring for 3 hours at -78°C more DIBAL was added (11ml, 11mmol) and the reaction allowed to warm to room temperature. Following a total reaction time of 24 hours the reaction was quenched with water (0.5ml). The reaction mixture was partitioned between DCM and water. The aqueous layer was separated, acidified (20ml, 1M HCl) and extracted with DCM. The organic extracts were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure to yield 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-ol as an off white solid (1.69g, 93%). ^{1}H-NMR; δ ($CDCl_3$), 7.40 (1H, t, J=7.9Hz), 7.19 (2H, d, J=7.8Hz), 7.16 (1H, t, J=7.3Hz), 7.08 (1H, d, J=7.7Hz), 7.01 (2H, d, J=7.9Hz), 6.96 (1H, dt, J=15.7, 5.0Hz), 6.69 (1H, d, J=15.7Hz), 6.66 (1H, d, J=7.8Hz), 4.36 (2H, dd, J=5.0, 1.4Hz), 3.58 (2H, d, J=7.2Hz), 3.04 (4H, bs), 2.36 (3H, s) and 1.96 (4H, bs); ^{13}C-NMR; δ ($CDCl_3$), 155.8, 154.7, 146.6, 137.9, 136.9, 134.8, 133.8, 129.5, 129.4, 129.3, 129.1, 121.1, 120.8, 62.6, 53.0, 52.8, 29.6, 23.4, 23.4 and 21.2.

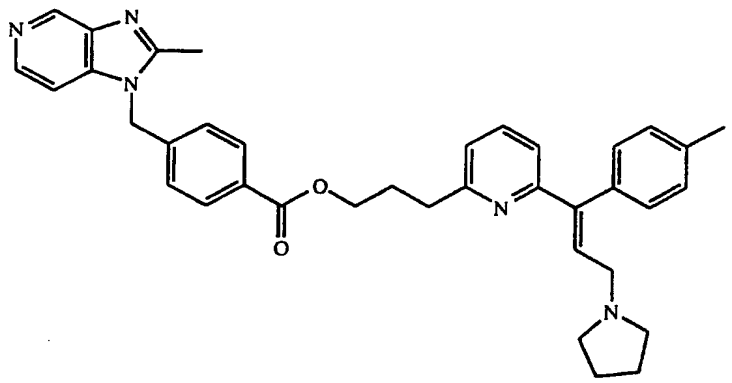
(c) 4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]prop-2E-enyl ester.

A solution of 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (310mg, 1.08mmol), 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-ol (300mg, 0.90mmol) and EDC (275mg, 1.44mmol) in DCM (10ml) was treated with DMAP (5mg) and stirred at room temperature for 96 hours. The solution was concentrated under reduced pressure and purified by column chromatography on silica-gel. Product was eluted with 5% methanol/DCM. Product containing fractions were combined and solvent removed to yield 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]prop-2E-enyl ester as a white foam (72mg, 15%). ^{1}H-NMR; δ ($CDCl_3$), 9.03 (1H, s), 8.37 (1H, d, J=5.5Hz), 8.08 (2H, d, J=8.4Hz), 7.44 (1H, t,

J=7.7Hz), 7.21 (2H, d, J=7.9Hz), 7.20 (1H, t, J=7.0Hz), 7.15 (1H, d, J=5.8Hz), 7.13 (2H, d, J=8.4Hz), 7.10 (1H, d, J=9.0Hz), 7.07 (2H, d, J=8.0Hz), 7.01 (1H, dt, J=15.5, 6.0Hz), 6.78 (1H, d, J=15.7Hz), 6.71 (1H, d, J=7.7Hz), 5.39 (2H, s), 5.03 (2H, d, J=1.4Hz), 3.30 (2H, d, J=7.0Hz), 2.67 (4H, br s), 2.60 (3H, s), 2.40 (3H, s) and 1.82 (4H, bs); ^{13}C-NMR; δ ($CDCl_3$), 165.5, 157.1, 153.5, 153.4, 142.2, 142.0, 140.3, 139.9, 139.8, 137.2, 136.8, 135.0, 132.9, 130.7, 130.3, 129.6, 129.2, 127.8, 126.2, 121.3, 120.5, 104.8, 65.0, 54.4, 53.9, 47.1, 23.4, 21.3 and 14.0.

Example 2

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]propyl ester.



(a) Methyl-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-propanoate.

Sodium borohydride (629mg, 16.56mmol) and tellurium (898mg, 7.04mmol) were heated in degassed ethanol (30ml) under an inert atmosphere at 80°C for 1 hour. The resulting suspension was cooled to room temperature, treated with degassed

ammonium chloride followed by a solution of methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylate (1.0g, 2.76mmol) in ethanol (10ml). The reaction was stirred at room temperature for 18 hours under an inert atmosphere. The reaction was opened to the air, stirred for 2 hours and then filtered through a pad of kieselguhr. The filtrate was concentrated under reduced pressure to leave a pink solid. The solid was triturated with DCM (X3). The combined washings were filtered and solvent removed under reduced pressure to yield methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-propanoate as a pink foam (1.084g, contaminated with some ethyl ester). ^{1}H-NMR; δ ($CDCl_3$), 7.47 (1H, t, J=7.6Hz), 7.26 (2H, d, J=6.9Hz), 7.00 (4H, m), 6.72 (1H, d, J=7.2Hz), 3.78 (2H, d, J=6.8Hz), 3.70 (3H, s), 3.30 (4H, bm), 3.18 (2H, t, J=8.2Hz), 2.88 (2H, t, J=7.2Hz), 2.45 (3H, s) and 2.14 (4H, bm).

(b) (E)-3-(6-[3-Pyrrolidino-1-{4-tolyl}-prop-1-enyl]-pyridin-2-yl)-propanol.

A solution of methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1-enyl]-pyridin-2-yl)-propanoate (206mg, 0.55mmol, mixture of methyl and ethyl esters) in THF (5ml) was cooled to -78°C and treated under an inert atmosphere with DIBAL (1.65ml of 1.0M solution in toluene, 1.65mmol). The reaction was stirred for 4 hours at -78°C and allowed to warm to room temperature. The reaction was quenched with water (2ml) and the product extracted into DCM (X3). The organic extracts were combined, dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield (E)-3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1-enyl]-pyridin-2-yl)-propanol as a pale brown gum (137mg, 74%). ^{1}H-NMR; δ ($CDCl_3$), 7.42 (1H, t, J=8.3Hz), 7.20 (2H, d, J=7.8Hz), 7.09 (2H, d, J=9.6Hz), 6.98 (2H, m), 6.73 (1H, d, J=7.6Hz), 3.70 (2H, t, J=7.3Hz), 3.18 (2H, d, J=6.9Hz), 2.97 (2H, t, J=7.3Hz), 2.52 (4H, bm), 2.39 (3H, s), 2.00 (2H, m) and 1.77 (4H, bm).

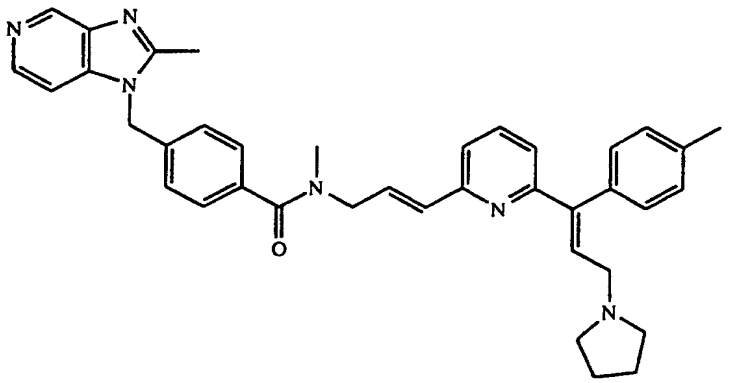
(c) 4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]propyl ester.

A solution of 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium

salt (551mg, 1.52mmol), (E)-3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-propanol (341mg, 1.02mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (311mg, 1.62mmol) in DCM (10ml) was treated with dimethylaminopyridine (5mg) and stirred at room temperature for 96 hours. The reaction mixture was partitioned between DCM and saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica-gel eluting with 10% methanol/DCM. Product containing fractions were combined and solvent removed to yield 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]propyl ester as a white foam (138mg, 23%). ^{1}H-NMR; δ ($CDCl_3$), 9.00 (1H, s), 8.33 (1H, d, J=5.5Hz), 7.96 (2H, d, J=8.3Hz), 7.35 (1H, t, J=7.7Hz), 7.18 (2H, d, J=7.8Hz), 7.10 (6H, m), 6.95 (1H, d, J=7.6Hz), 6.64 (1H, d, J=7.7Hz), 5.37 (2H, s), 4.36 (2H, t, J=6.5Hz), 3.27 (2H, d, J=7.0Hz), 2.90 (2H, t, J=7.3Hz), 2.65 (4H, m), 2.57 (3H, s), 2.36 (3H, s), 2.25 (2H, m) and 1.78 (4H, m); ^{13}C-NMR; δ ($CDCl_3$), 165.8, 160.0, 156.9, 153.5, 142.1, 141.9, 140.3, 139.8, 139.7, 137.1, 136.5, 135.1, 130.5, 130.5, 130.4, 129.6, 129.2, 126.1, 121.2, 119.8, 104.8, 64.8, 54.4, 53.8, 47.1, 34.6, 31.2, 28.0, 23.4, 21.2 and 14.0.

Example 3

N-Methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) 3-(6-[3-Pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal.

A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-ol (1.00g, 2.99mmol) in DCM (20ml) was treated portionwise with manganese dioxide (4g, 46mmol). The reaction mixture was stirred vigorously for 3 hours before filtration through a glass fibre pad. The filtrate was concentrated under reduced pressure to yield 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal as a brown solid (0.924g, 93%). ^{1}H -NMR; δ ($CDCl_3$), 9.87 (1H, d, J=9.5Hz), 7.55 (1H, t, J=7.5Hz), 7.50 (1H, d, J=15.5Hz), 7.33 (1H, d, J=8.0Hz), 7.21 (2H, d, J=8.5Hz), 7.18-7.13 (2H, m), 7.08 (2H, d, J=8.5Hz), 6.92 (1H, d, J=9.5Hz), 3.27 (2H, d, J=9.5Hz), 2.62-2.27 (4H, m), 2.39 (3H, s) and 1.81-1.77 (4H, m).

(b) Methyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

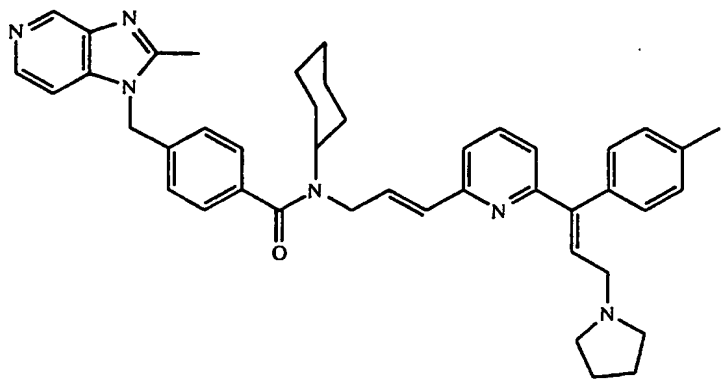
A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (230mg, 0.69mmol) in DCM (10ml) was treated with magnesium sulphate (1.25g) and methylamine (380µl of a 2M solution in THF, 0.76mmol). The reaction was stirred in the absence of light for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (10ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (30.6mg, 0.81mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with brine. The organics were dried over magnesium sulphate, filtered and concentrated to yield methyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (208mg, 87%). ^{1}H -NMR; δ ($CDCl_3$), 7.38 (1H, t, J=8.5Hz), 7.17-7.16 (3H, m), 7.09-7.04 (3H, m), 6.90 (1H, dt, J=16.0, 6.5Hz), 6.66 (1H, d, J=7.5Hz), 6.61 (1H, d, J=15.0Hz), 3.43 (2H, d, J=5.5Hz), 3.18 (2H, d, J=7.5Hz), 2.54-2.49 (4H, m), 2.47 (3H, s), 2.38 (3H, s) and 1.77-1.73 (4H, m).

(c) N-Methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of methyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (208mg, 0.60mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid dihydrochloride salt (204mg, 0.60mmol), EDC (172mg, 0.90mmol), HOAt (10mg, 0.07mmol) and N-methylmorpholine (132µl, 1.20mmol) in DMF (5ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-20% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown foam (222mg, 62%). ^{1}H-NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.37 (1H, d, J=5.5Hz), 7.44 (2H, d, J=8.1Hz), 7.42 (1H, t, J=7.7Hz), 7.20 (2H, d, J=7.8Hz), 7.17 (2H, d, J=5.5Hz), 7.08 (2H, d, J=7.9Hz), 7.08-7.00 (3H, m), 6.80-6.52 (3H, m), 5.34 (2H, s), 4.35 and 4.03 (2H, 2Xbs), 3.18 (2H, d, J=7.0Hz), 3.12 and 2.95 (3H, 2Xbs), 2.59 (3H, s), 2.51 (4H, bs), 2.39 (3H, s) and 1.75 (4H, bs); ^{13}C-NMR; δ ($CDCl_3$), 157.6, 153.4, 153.1, 142.1, 142.0, 141.4, 140.3, 139.8, 131.7, 129.7, 129.1, 127.7, 126.2, 121.2, 120.4, 104.8, 54.9, 54.2, 53.2, 47.0, 33.5, 23.5, 21.2 and 14.0.

Example 4

N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Cyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

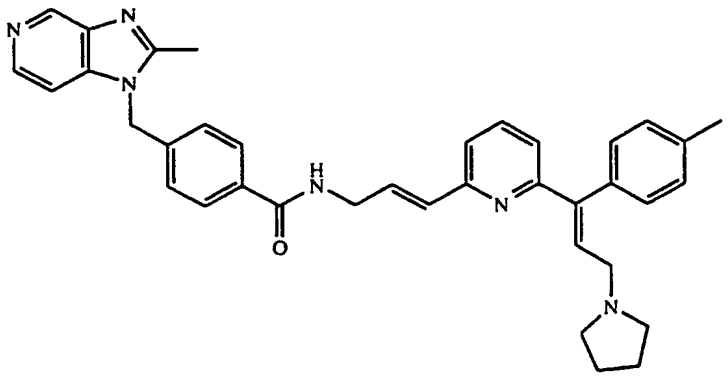
A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (463mg, 1.34mmol) in DCM (20ml) was treated with activated powdered 3Å molecular sieves (3g) and cyclohexylamine (175µl, 1.53mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (20ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (62mg, 1.64mmol). The reaction was stirred for 2.5 hours and solvent removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with brine. The organics were dried over magnesium sulphate, filtered and concentrated to yield cyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (530mg, 92%). ^{1}H -NMR; δ ($CDCl_3$), 7.40 (1H, t, J=8.0Hz), 7.22-7.17 (3H, m), 7.12-7.07 (3H, m), 6.92 (1H, dt, J=15.0, 6.0Hz), 6.68 (1H, d, J=8.0Hz), 6.62 (1H, d, J=16.0Hz), 3.49 (2H, dd, J=6.5, 0.5Hz), 3.18 (2H, d, J=8.0Hz), 2.56-2.50 (5H, m), 2.40 (3H, s), 1.94 (2H, bd, J=13.0Hz), 1.79-1.71 (6H, m), 1.66-1.60 (1H, m) and 1.33-1.06 (5H, m).

(b) N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-Pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of cyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (500mg, 1.20mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (348mg, 1.20mmol), EDC (246mg, 1.81mmol) and HOAt (15mg) in DMF (15ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-20% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown foam (555mg, 69%). ^{1}H-NMR; δ ($CDCl_3$), 9.03 (1H, s), 8.36 (1H, d, J=5.3Hz), 7.40 (1H, t, J=7.7Hz), 7.37 (2H, d, J=7.9Hz), 7.19 (2H, d, J=7.9Hz), 7.16-7.10 (2H, m), 7.08 (2H, d, J=7.9Hz), 7.10-6.85 (3H, m), 6.85-6.20 (3H, bm), 5.33 (2H, s), 4.45-3.40 (3H, bm), 3.22 (2H, d, J=6.9Hz), 2.58 (7H, bs), 2.38 (3H, s), 1.90-1.70 (8H, bm), 1.66-1.53 (3H, m) and 1.50-0.95 (3H, bm); ^{13}C-NMR; δ ($CDCl_3$), 157.4, 154.6, 153.5, 142.0, 141.4, 140.3, 139.8, 136.5, 133.7, 130.7, 130.4, 129.7, 129.0, 127.2, 126.4, 120.4, 119.5, 104.9, 54.8, 54.1, 47.1, 23.5, 21.2 and 14.0.

Example 5

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) 3-(6-[3-Pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-yl acetate.

Pyridine (110µl, 1.36mmol) was added to a solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-ol (227mg, 0.68mmol) in DCM (3ml) under an inert atmosphere. Acetyl chloride (72µl, 1.02mmol) was added and the reaction stirred for 18 hours at room temperature. The reaction mixture was partitioned between DCM and brine. The organic layer was separated, dried over sodium sulphate, filtered and concentrated under vacuum to leave a brown oil. The product was purified by column chromatography on silica gel eluting with 5% methanol/DCM. Product containing fractions were combined and solvent removed to yield 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-yl acetate as a brown gum (184mg, 73%). ^{1}H-NMR; δ ($CDCl_3$), 7.49 (1H, t, J=7.8Hz), 7.24 (2H, d, J=7.9Hz), 7.18-7.11 (2H, m), 7.06 (2H, d, J=7.9Hz), 6.91-6.66 (3H, m), 4.79 (2H, dd, J=5.4, 0.7Hz), 3.72 (2H, m), 3.20 (4H, bm), 2.40 (3H, s), 2.12 (3H, s) and 2.11-2.02 (4H, m).

(b) {3-(6-[3-Pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-azide.

A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-en-1-

yl acetate (136mg, 0.365mmol) in a mixture of THF/water (5:1, 5ml) was treated with sodium azide (28mg, 0.44mmol) and tetrakis(triphenylphosphine) palladium(0) (17mg, 0.015mmol). The reaction was stirred at room temperature for 18 hours. Solvent was removed under reduced pressure to leave a dark brown residue. The product was purified by column chromatography on silica-gel eluting with 5% methanol/DCM. Product containing fractions were combined and solvent removed under reduced pressure to yield {3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-azide as a brown gum (110mg, 85%). ^{1}H-NMR; δ ($CDCl_3$), 7.67 (1H, m), 7.56 (1H, m), 7.40 (2H, m), 7.24 (2H, d, J=8.2Hz), 7.19 (1H, t, J=6.8Hz), 7.10 (2H, m), 6.91 (1H, dt, J=15.8, 6.6Hz), 6.73 (2H, m), 4.02 (2H, d, J=8.8Hz), 3.35 (2H, m), 2.70 (2H, m), 2.41 (3H, s) and 1.82 (4H, m).

(c) {3-(6-[3-Pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of {3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-azide (154mg, 0.43mmol) in methanol (10ml) was treated with tin (II) chloride (163mg, 0.86mmol). The reaction showed a slight exotherm and darkened in colour. After 1 hour solvent was removed under reduced pressure to leave a green gum. The residue was treated with sodium hydroxide solution (5M) and the product extracted (X4) with diethyl ether. The combined organic extracts were combined, dried over magnesium sulphate, filtered and solvent removed to yield {3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown gum (77.5mg, 54%). ^{1}H-NMR; δ ($CDCl_3$), 7.43 (1H, t, J=8.1Hz), 7.21 (3H, m), 7.09 (3H, m), 6.99 (1H, dt, J=16.3, 6.3Hz), 6.69 (1H, d, J=8.0Hz), 6.61 (1H, dt, J=15.6, 1.4Hz), 3.56 (2H, dd, J=5.8, 1.3Hz), 3.21 (2H, d, J=9.6Hz), 2.56 (4H, m), 2.40 (3H, s), 1.79 (4H, s) and 1.71 (2H, bs).

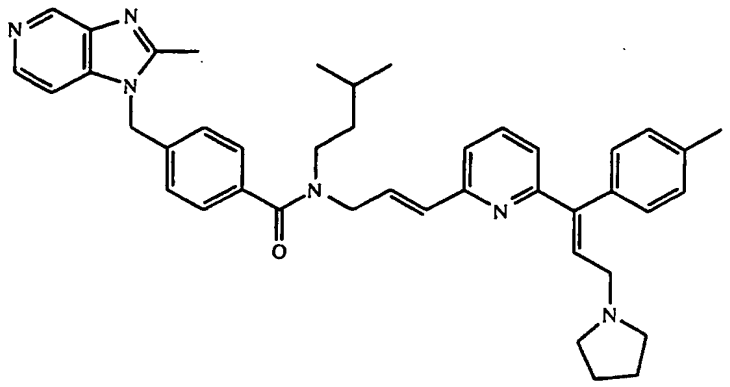
(d) 4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

DMF (3ml) was added to a mixture of {3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (77.5mg, 0.23mmol), 4-(1H-2-methyl-imidazo[4,5-

c]pyridin-1-ylmethyl)}benzoic acid sodium salt (101mg, 0.28mmol), EDC (54mg, 0.28mmol) and HOAt (38mg, 0.28mmol). N-Methylmorpholine (102µl, 0.93mmol) was added and the suspension stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulphate, filtered and concentrated under reduced pressure to a brown gum. The product was purified by column chromatography on silica-gel eluting with 5-20% methanol/DCM. Product containing fractions were combined and solvent removed to yield 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a pale brown glass (33.6 mg, 24%). ^{1}H-NMR; δ (MeOD), 8.84 (1H, s), 8.29 (1H, d, J=5.7Hz), 7.86 (2H, d, J=8.3Hz), 7.52 (1H, d, J=5.7Hz), 7.51 (1H, t, J=7.8Hz), 7.22 (5H, m), 7.04 (2H, d, J=8.0Hz), 6.98 (1H, t, J=7.0Hz), 6.84 (1H, dt, J=15.8, 5.6Hz), 6.72 (1H, d, J=8.0Hz), 6.66 (1H, d, J=15.8Hz), 5.60 (2H, s), 4.20 (2H, dd, J=5.7,1.2Hz), 3.24 (2H, d, J=7.0Hz), 2.63 (3H, s), 2.57 (4H, m), 2.37 (3H, s) and 1.76 (4H, m); ^{13}C-NMR; δ (MeOD), 167.8, 157.2, 155.4, 154.5, 142.9, 141.0, 140.8, 139.7, 139.2, 139.1, 137.2, 136.8, 134.9, 134.0, 130.6, 130.6, 129.3, 129.3, 128.8, 128.8, 127.8, 127.7, 126.5, 120.7, 119.7, 106.0, 54.0, 53.5, 53.3, 46.5, 41.0, 22.7, 19.9, 19.8 and 12.4.

Example 6

N-(3-Methyl-but-1-yl)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) (3-Methyl-but-1-yl)-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

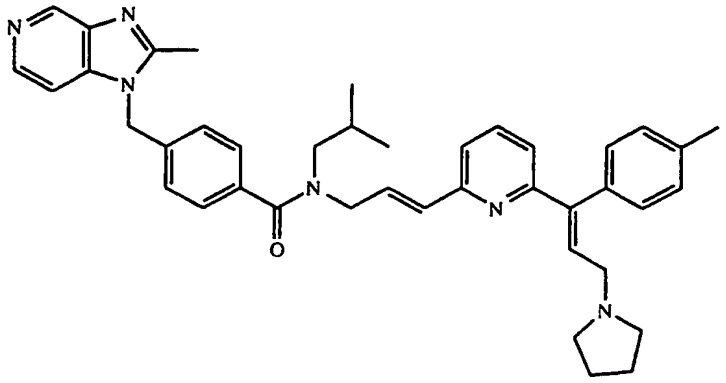
A solution of (E)-3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2-enal (345mg, 1.04mmol) in DCM (20ml) was treated with activated powdered 3Å molecular sieves (2g) and isoamylamine (133µl, 1.14mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (20ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (39mg, 1.04mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate solution. The organics were dried over anhydrous sodium sulphate, filtered and concentrated to yield (3-methyl-but-1-yl)-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as an orange oil (388mg, 92%). ^{1}H -NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.9Hz), 7.20 (3H, m), 7.10 (3H, m), 6.93 (1H, dt, J=6.0, 3.3Hz), 6.68 (1H, d, J=8.1Hz), 6.63 (1H, d, J=15.8Hz), 3.48 (2H, dd, J=6,2, 1.3Hz), 3.18 (2H, d, J=7.0Hz), 2.69 (2H, t, J=7.3Hz), 2.53 (4H, m), 2.40 (3H, s), 1.77 (5H, m), 1.65 (2H, q, J=6.8Hz) and 0.92 (6H, d, J=6.8Hz).

(b) N-(3-Methyl-but-1-yl)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of (3-methyl-but-1-yl)-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (383mg, 0.95mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid dihydrochloride salt (323mg, 0.95mmol), EDC (274mg, 1.43mmol), N-methylmorpholine (209µl, 1.90mmol) and HOAt (20mg) in DMF (10ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-15% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-(3-methyl-but-1-yl)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a pale brown foam (313mg, 51%). ^{1}H-NMR; δ ($CDCl_3$), 9.01 (1H, s), 8.35 (1H, d, J=5.7Hz), 7.51-7.42 (3H, m), 7.27-7.05 (10H, m), 6.82-6.73 (2H, m), 5.37 (2H, s), 4.34 (1H, m), 4.05 (1H, bs), 3.55 (2H, d, J=5.9Hz), 3.25 (1H, m), 3.00 (4H, m), 2.60 (3H, s), 2.40 (3H, s), 1.97 (4H, bs), 1.57-1.40 (4H, bm) 0.95 (4H, d, J=5.5Hz) and 0.70 (2H, m); ^{13}C-NMR; δ ($CDCl_3$), 170.8, 156.1, 154.2, 153.5, 142.0, 141.8, 140.3, 139.8, 137.8, 137.0, 136.8, 136.5, 136.3, 136.0, 133.9, 132.3, 131.0, 130.0, 129.4, 129.3, 127.5, 127.4, 126.2, 121.4, 121.3, 121.0, 120.4, 104.9, 77.4, 53.7, 53.2, 53.0, 50.5, 47.0, 46.9, 46.2, 43.7, 37.3, 35.8, 26.2, 25.5, 23.4, 23.3, 22.5, 22.2, 21.2 and 14.0.

Example 7

N-*iso*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a)*iso*-Butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

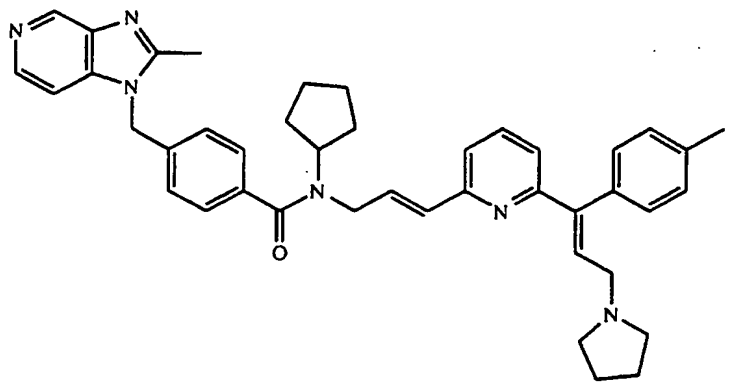
A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (369mg, 1.11mmol) in DCM (20ml) was treated with activated powdered 3Å molecular sieves (2g) and *iso*-butylamine (120µl, 1.22mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (20ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (40mg, 1.00mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with brine. The organics were dried over anhydrous magnesium sulphate, filtered and concentrated to yield *iso*-butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as an orange oil (300mg, 80%). ^{1}H -NMR; δ ($CDCl_3$), 7.38 (1H, t, J=8.0Hz), 7.20-7.17 (3H, m), 7.10-7.05 (3H, m), 6.91 (1H, dt, J=16.0, 6.5Hz), 6.67 (1H, d, J=8.0Hz), 6.62 (1H, d, J=14.0Hz), 3.45 (2H, d, J=4.0Hz), 3.19 (2H, d, J=7.5Hz), 2.57-2.52 (4H, m), 2.48 (2H, d, J=6.0Hz), 2.38 (3H, s), 1.81-1.74 (5H, m), 1.23 (1H, s) and 0.92 (6H, d, J=7.5Hz).

(b) N-(*iso*-Butyl)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of *iso*-butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (300mg, 0.77mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid dihydrochloride salt (262mg, 0.77mmol), EDC (221mg, 1.16mmol), N-methylmorpholine (270µl, 1.54mmol) and HOAt (15mg) in DMF (10ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-20% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-(*iso*-butyl)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a pale brown foam (264mg, 54%). ^{1}H-NMR; δ ($CDCl_3$), 9.03 (1H, s), 8.38 (1H, d, J=5.5Hz), 7.44 (1H, t, J=7.8Hz), 7.41 (2H, d, J=8.1Hz), 7.22-6.98 (9H, m), 6.87-6.40 (3H, m), 5.35 (2H, s), 4.37 (0.64H, d, J=5.2Hz), 4.05 (1.36H, d, J=4.1Hz), 3.41 (1.32H, d, J=7.5Hz), 3.19 (2H, d, J=6.6Hz), 3.11 (0.68H, d, J=7.0Hz), 2.60 (3H, s), 2.53 (4H, bs), 2.39 (3H, s), 2.20-1.85 (1H, m), 1.77 (4H, bs), 0.97 (4H, d, J=6.6Hz) and 0.94 (2H, d, J=6.8Hz); ^{13}C-NMR; δ ($CDCl_3$), 171.3 157.5, 153.3, 142.1, 142.0, 140.3, 139.8, 137.0, 136.9, 136.6, 136.1, 135.2, 133.0, 131.5, 129.7, 129.3, 129.1, 128.9, 128.0, 127.4, 126.2, 121.1, 120.4, 104.8, 55.7, 54.7, 54.1, 51.8, 51.2, 47.0, 46.1, 26.6, 23.4, 21.2, 20.1, 19.8 and 14.0.

Example 8

N-Cyclopentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Cyclopentyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

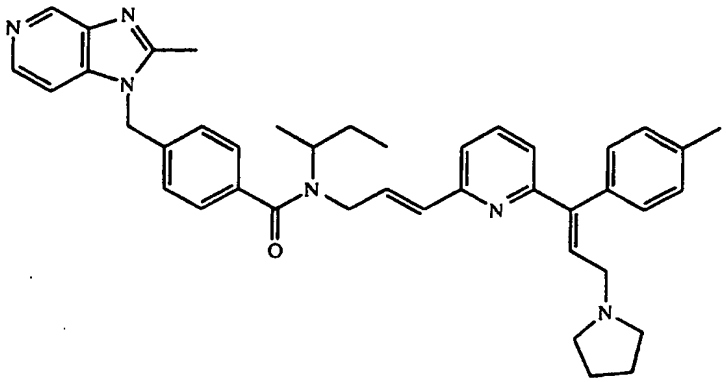
A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (340mg, 1.02mmol) in DCM (20ml) was treated with activated powdered 3Å molecular sieves (2g) and cyclopentylamine (111µl, 1.12mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (20ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (37mg, 0.98mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated to yield cyclopentyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (374mg, 95%). ^{1}H - NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.8Hz), 7.20 (3H, m), 7.09 (3H, m), 6.93 (1H, m), 6.68 (1H, d, J=7.8Hz), 6.63 (1H, d, J=15.5Hz), 3.46 (2H, dd, J=6.1, 1.3Hz), 3.18 (3H, m), 2.53 (4H, m), 2.40 (3H, s), 1.89 (2H, m), 1.77 (4H, m), 1.71 (2H, m), 1.56 (2H, m) and 1.37 (2H, m).

(b) N-Cyclopentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of cyclopentyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (370mg, 0.92mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid dihydrogen chloride salt (314mg, 0.92mmol), EDC (265mg, 1.38mmol) N-methylmorpholine (202µl, 1.82mmol) and HOAt (20mg) in DMF (10ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated sodium bicarbonate solution. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-15% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-cyclopentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown foam (74mg, 12%). ^{1}H-NMR; δ ($CDCl_3$), 9.03 (1H, s), 8.38 (1H, d, J=5.4Hz), 7.42 (3H, m), 7.19-7.07 (9H, m), 6.74 (3H, m), 5.35 (2H, s), 4.16 (2H, bs), 3.18 (2H, d, J=7.0Hz), 2.60 (3H, s), 2.52 (4H, m), 2.39 (3H, s), 2.23 (1H, m) and 1.75-1.50 (12H, bm); ^{13}C-NMR; δ ($CDCl_3$), 157.4, 153.5, 142.0, 141.9, 141.4, 140.3, 139.8, 137.4, 136.5, 136.4, 136.0, 135.4, 131.4, 130.6, 129.7, 129.0, 127.4, 126.3, 120.7, 119.6, 104.8, 60.6, 54.8, 54.1, 47.0, 30.1, 29.6, 24.0 23,4, 23.2, 21.2 and 14.0.

Example 9

N-(R,S) *sec*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-(E)-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2-enyl}-benzamide.



(a) (R,S)-*sec*-Butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

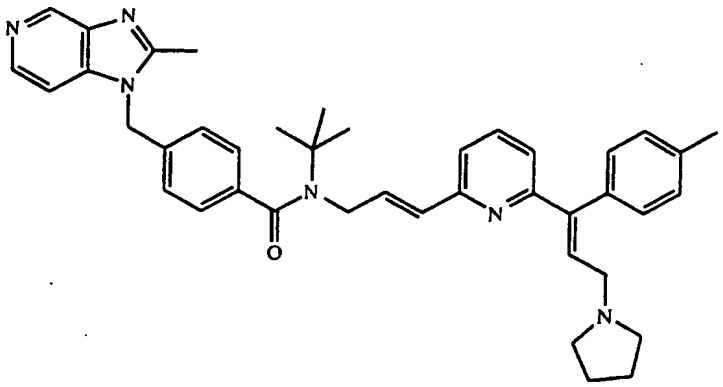
A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (217mg, 0.653mmol) in DCM (10ml) was treated with activated powdered 3Å molecular sieves (1g) and (R,S)-*sec*-butylamine (225µl, 2.16mmol). The reaction was stirred for 36 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (20ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (62mg, 1.64mmol). The reaction was stirred for 2.5 hours and solvent removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with brine. The organics were dried over magnesium sulphate, filtered and concentrated to yield (R,S)-*sec*-butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as an orange oil (530mg, 92%). ^{1}H -NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.8Hz), 7.26-7.19 (3H, m), 7.15-7.08 (3H, m), 6.93 (1H, dt, J=15.7, 6.1Hz), 6.68 (1H, d, J=8.2Hz), 6.64 (1H, dt, J=15.9, 1.4Hz), 3.58-3.41 (2H, m), 3.19 (2H, d, J=6.9Hz), 2.77-2.64 (1H, m), 2.57-2.52 (4H, m), 2.41 (3H, s), 1.82-1.76 (4H, m), 1.64-1.49 (1H, m), 1.47-1.33 (1H, m), 1.28 (1H, s), 1.09 (3H, d, J=6.3Hz) and 0.93 (3H, t, J=7.4Hz).

(b) N-(R,S)-*sec*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of (R,S)-*sec*-butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (225mg, 0.578mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (167mg, 0.578mmol), EDC (166mg, 0.867mmol) and HOAt (10mg) in DMF (10ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-50% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-(R,S)-*sec*-butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown oil (218mg, 59%). ^{1}H-NMR; δ ($CDCl_3$), 9.01 (1H, bs), 8.34 (1H, bs), 7.39 (1H, t, J=7.8Hz), 7.37-7.34 (2H, m), 7.20-6.29 (12H, bm), 5.32 (2H, s), 4.54-3.60 (3H, bm), 3.16 (2H, d, J=6.9Hz), 2.57 (3H, bs), 2.50 (4H, bm), 2.36 (3H, s), 1.73 (4H, bm) and 1.70-0.68 (8H, bm); ^{13}C-NMR; δ ($CDCl_3$), 171.2, 170.9, 157.1, 154.0, 153.2, 152.9, 141.5, 141.3, 141.1, 139.9, 139.4, 137.7, 137.0, 136.4, 136.1, 135.7, 135.1, 131.6, 130.6, 130.3, 129.9, 129.3, 128.6, 127.0, 126.0, 120.3, 119.4, 119.1, 104.6, 56.2, 54.3, 53.7, 52.2, 47.2, 46.6, 41.8, 27.6, 26.9, 23.1, 20.8, 19.5, 18.0, 13.6 and 10.7.

Example 10

N-*tert*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) *tert*-Butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (323mg, 0.927mmol) in DCM (20ml) was treated with activated powdered 3Å molecular sieves (2g) and *tert*-butylamine (350µl, 3.21mmol). The reaction was stirred for 1 week, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (20ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (35mg, 0.93mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with brine. The organics were dried over anhydrous magnesium sulphate, filtered and concentrated to yield *tert*-butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as an orange oil (439mg, crude). ^{1}H -NMR; δ ($CDCl_3$), 7.40 (1H, t, J=7.5Hz), 7.24-7.16 (3H, m), 7.13-7.06 (3H, m), 6.94 (1H, dt, J=7.5, 6.6Hz), 6.70-6.60 (2H, m), 3.43 (2H, dd, J=5.5, 1.0Hz), 3.19 (2H, d, J=7.0Hz), 2.57-2.50 (4H, m), 2.39 (3H, s), 1.80-1.73 (4H, m) and 1.16 (9H, s).

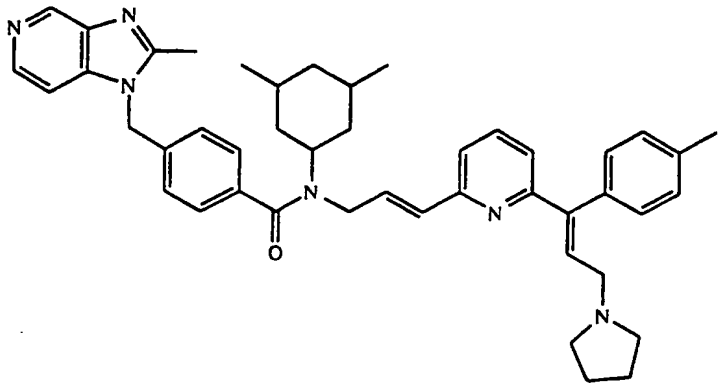
(b) N-*tert*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-

pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of *tert*-butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (439mg, 1.13mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (326mg, 1.13mmol), EDC (324mg, 1.69mmol) and HOAt (15mg) in DMF (10ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-25% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-*tert*-butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown oil (75mg, 11%). ^{1}H-NMR; δ ($CDCl_3$), 9.01 (1H, d, J=0.7Hz), 8.35 (1H, d, J=5.5Hz), 7.46 (1H, t, J=7.8Hz), 7.35 (2H, d, J=8.2Hz), 7.24-7.15 (4H, m), 7.07 (2H, d, J=8.0Hz), 7.03-6.99 (3H, m), 6.78-6.67 (2H, m), 6.43 (1H, bd, J=15.8Hz), 5.34 (2H, s), 4.10 (2H, d, J=3.6Hz), 3.48 (2H, d, J=6.7Hz), 2.90 (4H, bs), 2.58 (3H, s), 2.40 (3H, s), 1.92 (4H, bm) and 1.58 (9H, s); ^{13}C-NMR; δ ($CDCl_3$), 172.7, 156.4, 153.7, 153.6, 142.0, 141.8, 140.3, 139.8, 139.3, 137.7, 137.0, 135.7, 133.3, 130.7, 129.4, 129.3, 126.9, 126.1, 121.2, 120.5, 104.9, 57.8, 53.9, 53.4, 49.2, 47.0, 28.7, 23.4, 21.2 and 14.0.

Example 11

N-3,5-Dimethylcyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) 3,5-Dimethylcyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (206mg, 0.62mmol) in DCM (10ml) was treated with activated powdered 3Å molecular sieves (1g) and 3,5-dimethylcyclohexylamine (169mg, 1.36mmol). The reaction was stirred for 36 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (10ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (30mg, 0.79mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with brine. The organics were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica-gel, eluting with 10-20% methanol/DCM. Product containing fractions were combined and solvent removed under reduced pressure to yield 3,5-dimethylcyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (50mg). ^{1}H -NMR; δ ($CDCl_3$), 7.44 (1H, t, J=8.0Hz), 7.26-7.19 (3H, m), 7.16-7.08 (3H, m), 6.94 (1H, dt, J=16.0, 6.5Hz), 6.71-6.62 (2H, m), 3.47 (2H, dd, J=6.5, 1.0Hz), 3.20 (2H, d, J=7.0Hz), 3.06-3.01 (1H, m),

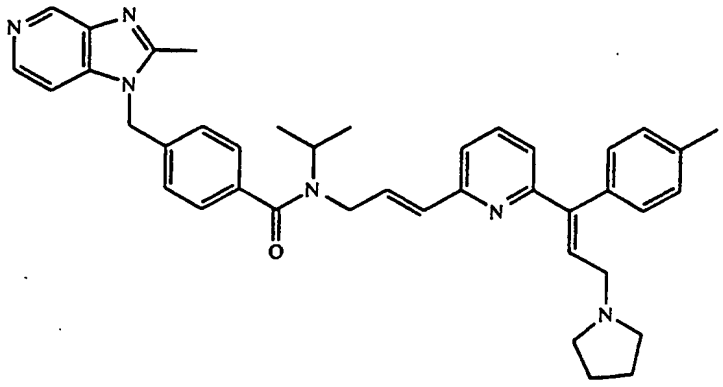
2.59-2.51 (4H, m), 2.42 (3H, s), 1.84-1.61 (10H, m), 1.02 (2H, dt, J=13.5, 2.5Hz), 0.90 (6H, d, J=6.0Hz) and 0.64-0.49 (1H, m).

(b) N-3,5-Dimethylcyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of 3,5-dimethylcyclohexyl-(E)-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2-enyl}-amine (50mg, 0.11mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (60mg, 0.20mmol), EDC (33mg, 0.17mmol) and HOAt (5mg) in DMF (10ml) was stirred at room temperature for 12 days. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown oil. The product was purified by column chromatography on silica-gel eluting with 10-25% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-3.5-dimethylcyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N--{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a yellow oil (43mg, 54%). ^{1}H-NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.35 (1H, bd, J=4.5Hz), 7.41 (1H, t, J=7.8Hz), 7.38 (2H, d, J=8.1Hz), 7.22-6.99 (9H, m), 6.78 (1H, dt, J=15.6, 5.0Hz), 6.69 (1H, d, J=7.8Hz), 6.56-6.33 (1H, m), 5.34 (2H, s), 4.50-4.10 (1H, bm), 4.25 (2H, bd, J=3.6Hz), 3.19 (2H, d, J=6.9Hz), 2.58 (3H, s), 2.53 (4H, bs), 2.39 (3H, s), 2.10-1.60 (5H, bm), 1.76 (4H, bm), 1.34-1.21 (2H, m), 0.95-0.66 (1H, m) and 0.84 (6H, bd, J=6.3Hz); ^{13}C-NMR; δ ($CDCl_3$), 157.4, 153.5, 142.1, 142.0, 141.6, 140.3, 139.8, 137.9, 136.9, 136.7, 135.9, 135.3, 129.7, 129.1, 127.4, 126.2, 120.8, 119.9, 104.9, 54.8, 54.1, 47.0, 36.9, 28.3, 23.5, 22.5, 21.3 and 14.0.

Example 12

N-*iso*-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) *iso*-Propyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (415mg, 1.25mmol) in DCM (20ml) was treated with activated powdered 3Å molecular sieves (2g) and *iso*-propylamine (427µl, 5.00mmol). The reaction was stirred for 96 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (10ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (45mg, 1.18mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with saturated sodium bicarbonate. The organics were dried over sodium sulphate, filtered and concentrated under reduced pressure to yield *iso*-propyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (413mg, 93%). ^{1}H -NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.7Hz), 7.23-6.88 (7H, bm), 6.65 (2H, m), 3.47 (2H, d, J=4.9Hz), 3.19 (2H, J=6.9Hz), 2.92 (1H, m), 2.53 (4H, m), 2.41 (3H, s), 1.77 (4H, m) and 1.12 (6H, d, J=6.3Hz).

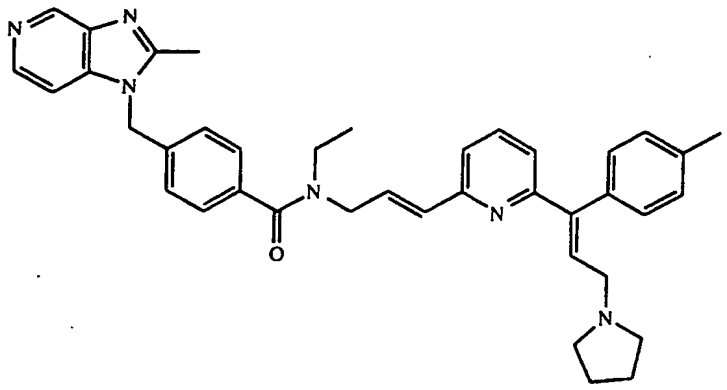
(b) N-*iso*-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-

pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of *iso*-propyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (405mg, 1.08mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid dihydrochloride salt (367mg, 1.08mmol), EDC (311mg, 1.62mmol), N-methylmorpholine (238µl, 2.16mmol) and HOAt (20mg) in DMF (10ml) was stirred at room temperature for 8 days. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated sodium bicarbonate solution. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown oil. The product was purified by column chromatography on silica-gel eluting with 10-15% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-*iso*-propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a pale brown foam (180mg, 27%). ^{1}H-NMR; δ (MeOD), 8.74 (1H, s), 8.19 (1H, d, J=5.0Hz), 7.46 (2H, t, J=7.8Hz), 7.32-6.58 (13H, bm), 5.49 (2H, s), 4.15-3.94 (3H, bm), 3.49 (2H, d, J=6.5Hz), 2.87 (4H, bs), 2.54 (3H, s), 2.27 (3H, s), 1.79 (4H, m) and 1.21-1.11 (6H, m); ^{13}C-NMR; δ (MeOD), 173.1, 157.9, 156.8, 156.1, 147.0, 142.4, 142.2, 141.1, 140.5, 139.2, 138.6, 138.4, 137.9, 135.5, 133.0, 132.7, 132.3, 130.7, 130.5, 128.2, 128.1, 124.7, 122.4, 121.7, 107.5, 54.9, 54.8, 52.5, 47.9, 43.2, 24.0, 21.3, 20.5 and 13.9.

Example 13

N-Ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Ethyl)-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (449mg, 1.35mmol) in DCM (20ml) was treated with magnesium sulphate (2g) and ethylamine (745µl of a 2.0M solution inTHF, 1.49mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (50mg, 1.32mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield ethyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (469mg, 98%). ^{1}H - NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.8Hz), 7.20 (3H, m), 7.09 (3H, m), 6.94 (1H, dt, J=15.8, 6.0Hz), 6.66 (2H, m), 3.49 (2H, dd, J=6.1, 1.4Hz), 3.19 (2H, d, J=7.0Hz), 2.74 (2H, q, J=7.1Hz), 2.53 (4H, bs), 2.40 (3H, s), 1.77 (4H, m) and 1.16 (3H, t, J=7.1Hz).

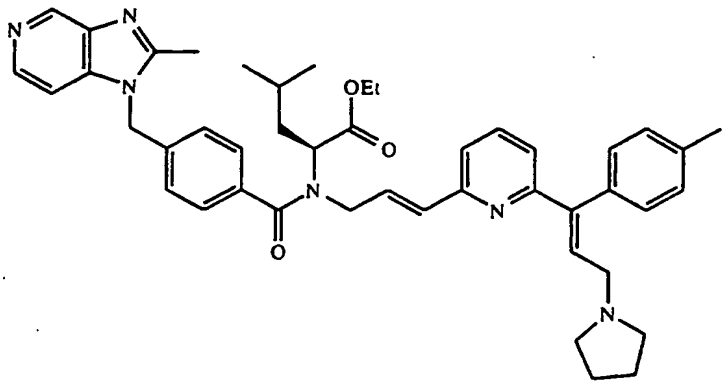
(b) N-Ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-

yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of ethyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (460mg, 1.27mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (368mg, 1.27mmol), EDC (360mg, 1.91mmol), N-methylmorpholine (279µl, 2.54mmol) and HOAt (20mg) in DMF (15ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated sodium bicarbonate solution. The organics were separated, dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown oil. The product was purified by column chromatography on silica-gel eluting with 5-10% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown gum (365mg, 47%). ^{1}H-NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.37 (1H, d, J=5.6Hz), 7.45 (3H, m), 7.24-7.17 (4H, m), 7.07 (5H, m), 6.75-6.49 (3H, bm), 5.35 (2H, s), 4.36 (1H, bs), 4.04 (1H, bs), 3.58 (2H, m). 3.34 (2H, d, J=6.7Hz), 2.72 (4H, bs), 2.60 (3H, s), 2.40 (3H, s), 1.84 (4H, bs) and 1.25-1.13 (3H, bm); ^{13}C-NMR; δ 170.8, 153.6, 142.1, 142.0, 139.9, 137.5, 137.0, 136.4, 134.8, 129.6, 129.4, 127.6, 121.3, 104.9, 77.3, 54.4, 53.8, 50.8, 47.1, 23.5, 21.3 and 14.1.

Example 14

(S)-4-Methyl-2-([4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-benzoyl]-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-amino)-pentanoic acid ethyl ester.



(a) (S)-4-Methyl-1-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-aminopentanoic acid ethyl ester.

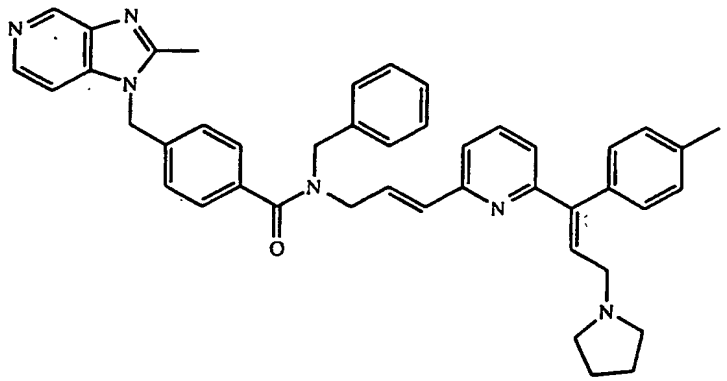
A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (420mg, 1.26mmol) in DCM (20ml) was treated with powdered 3Å molecular sieves (2g) and L-leucine ethyl ester (221mg, 1.39mmol). The reaction was stirred for 120 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (50mg, 1.31mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield (S)-4-methyl-1-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-aminopentanoic acid ethyl ester as a brown oil (585mg, 94%). ^{1}H -NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.8Hz), 7.23-7.06 (6H, bm), 6.83-6.61 (3H, m), 4.20 (3H, m), 3.47-3.22 (2H, m), 3.18 (2H, d, J=6.9Hz), 2.52 (4H, m), 2.41 (3H, s), 1.77 (4H, m), 1.51 (1H, t, J=7.2Hz), 1.27 (5H, m) and 0.97-0.90 (6H, m).

(b) (S)-4-Methyl-2-([4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-benzoyl]-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-amino)-pentanoic acid ethyl ester.

A solution of (S)-4-methyl-1-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-aminopentanoic acid ethyl ester (570mg, 1.20mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid dihydrochloride salt (408mg, 1.20mmol), EDC (345mg, 1.80mmol), N-methylmorpholine (264µl, 2.40mmol) and HOAt (20mg) in DMF (10ml) was stirred at room temperature for 8 days. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated sodium bicarbonate solution. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown oil. The product was purified by column chromatography on silica-gel eluting with 5-12% methanol in DCM. Product containing fractions were combined and solvent removed to yield (S)-4-methyl-2-([4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-benzoyl]-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-amino)-pentanoic acid ethyl ester as a brown oil (58mg, 8%). ^{1}H -NMR; δ (MeOD), 8.65 (1H, s), 8.08 (1H, d, J=5.6Hz), 7.39 (1H, t, J=7.7Hz), 7.33 (1H, d, J=5.6Hz), 7.29 (1H, d, J=7.7Hz), 7.25 (1H, d, J=7.8Hz), 7.10-7.03 (4H, m), 6.96 (1H, d, J=7.9Hz), 6.90 (1H, m), 6.82-6.74 (1H, m), 6.70 (1H, d, J=7.8Hz), 6.61 (1H, d, J=7.6Hz), 6.52 and 6.48 (1H, 2 x s), 6.28 (1H, d, J=15.6Hz), 5.42 and 5.39 (2H, 2 x s), 4.47 and 4.16 (1H, 2 x m), 3.96-3.91 (4H, m), 3.95 (1H, d, J=7.0Hz), 3.93 (1H, d, J=7.0Hz), 2.92 (2H, bs), 2.87 (2H, bs), 2.44 and 2.43 (3H, 2 x s), 2.19 and 2.17 (3H, 2 x s), 1.82-1.70 (4H, m), 1.61-1.53 (2H, m), 1.08-1.00 (4H, m), 0.76 and 0.74 (4H, 2 x d, J=6.5Hz), 0.52 (1H, d, J=6.3Hz) and 0.39 (1H, d, J=6.2Hz); ^{13}C-NMR; δ (MeOD), 174.0, 172.6, 172.1, 158.0, 157.8, 156.8, 155.9, 155.2, 147.7, 147.5, 142.4, 141.1, 140.5, 139.3, 139.2, 139.1, 138.5, 127.2, 137.0, 135.4, 135.2, 133.8, 133.1, 131.4, 131.3, 130.6, 130.5, 128.6, 128.5, 128.3, 128.2, 124.2, 123.5, 122.6, 121.9, 107.5, 62.9, 62.4, 61.6, 58.2, 54.7, 52.4, 48.0, 46.4, 39.2, 39.1, 26.3, 25.4, 24.0, 23.4, 22.9, 22.4, 22.0, 21.3, 14.6, 14.4 and 13.9.

Example 15

N-Benzyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Benzyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

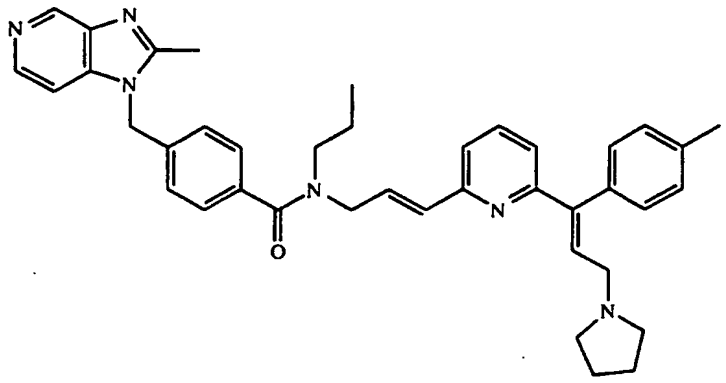
A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (500mg,1.50 mmol) in DCM (20ml) was treated with powdered 3Å molecular sieves (2.0g) and benzylamine (181µl, 1.65mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as an oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (57mg, 1.49mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield benzyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (658mg, ~100%). ^{1}H -NMR; δ ($CDCl_3$), 7.46-7.20 (14H, m), 6.99-6.91 (1H, m), 3.88 (2H, s), 3.52 (2H, dd, J=5.6 and 1.3Hz), 3.20 (2H, d, J=7.0Hz), 2.54 (4H, bs), 2.41 (2H, s) and 1.78 (4H, bs).

(b) N-Benzyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

A solution of benzyl-(E)-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2-enyl}-amine (645mg, 1.52mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (440mg, 1.52mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (437mg, 2.28mmol) and HOAt (20mg) in DMF (20ml) was stirred at room temperature for 48 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 5-10% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-benzyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as an orange gum (245mg, 24%). ^{1}H-NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.37 (1H, d, J=5.6Hz), 7.49 (3H, m), 7.36 (4H, m), 7.22 (5H, m), 7.09 (5H, m), 6.74-6.49 (3H, m), 5.37 (2H, bs), 4.83 (1H, m), 4.59 (1H, m), 4.31 (1H, m), 3.98 (1H, m), 3.39 (2H, m), 2.77 (4H, m), 2.60 (3H, s), 2.41 (3H, s) and 1.87 (4H, m); ^{13}C-NMR; δ ($CDCl_3$), 171.3, 156.8, 156.6, 154.1, 153.5, 153.3, 142.0, 141.8, 140.3, 139.7, 137.0, 136.8, 136.5, 136.3, 136.1, 134.5, 133.0, 131.8, 129.5, 129.3, 129.1, 128.9, 128.7, 128.3, 127.8, 127.6, 126.7, 126.3, 121.4, 121.2, 120.7, 120.2, 104.8, 54.2, 54.0, 53.6, 53.5, 51.9, 49.7, 47.6, 46.9, 46.4, 46.0, 29.6, 23.3, 21.2 and 14.0.

Example 16

N-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Propyl)-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

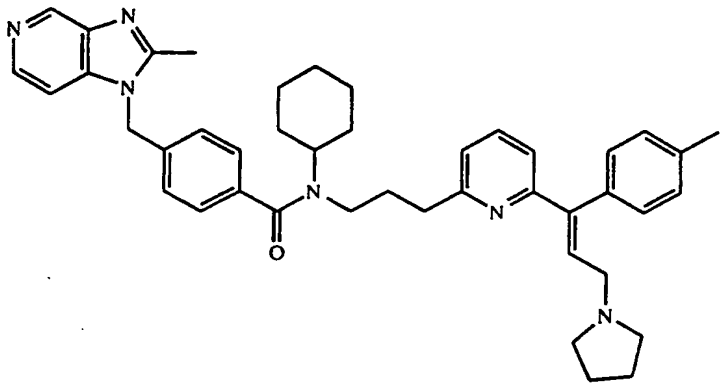
A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (500mg, 1.50mmol) in DCM (20ml) was treated with anhydrous magnesium sulphate (2g) and propylamine (136µl, 1.65mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (55mg, 1.45mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield propyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (542mg, 96%). ^{1}H -NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.8Hz), 7.23-7.07 (6H, m), 7.06-6.90 (1H, m), 6.69 (2H, m), 3.48 (2H, dd, J=6.1 and 1.3Hz), 3.19 (2H, d, J=7.0Hz), 2.66 (2H, t, J=7.2Hz), 2.54 (4H, bs), 2.41 (3H, s), 1.80-1.75 (4H, m), 1.63-1.49 (2H, m), 0.96 (3H, t, J=7.4Hz).

(b) N-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

A solution of propyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (530mg, 1.41mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (408mg, 1.41mmol), EDC (406mg, 2.12mmol) and HOAt (20mg) in DMF (20ml) was stirred at room temperature for 48 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 5-10% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as an orange foam (308mg, 35%). ^{1}H -NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.38 (1H, d, J=5.4Hz), 7.45 (3H, m), 7.24-7.06 (9H, bm), 6.75-6.48 (3H, bm), 5.36 (2H, s), 4.36 (1H, m), 4.05 (1H, m), 3.52 (1H, m), 3.38 (2H, d, J=6.6Hz), 3.23 (1H, m), 2.77 (4H, bs), 2.60 (3H, s), 2.40 (3H, s), 1.87 (4H, bs), 1.69 (2H, m), and 0.97-0.75 (3H, m); ^{13}C-NMR; δ ($CDCl_3$), 171.0, 156.9, 153.6, 142.0, 141.9, 140.3, 139.8, 137.4, 137.0, 136.8, 136.3, 134.6, 132.7, 131.4, 129.7, 129.5, 129.3, 127.7, 127.5, 126.3, 121.3, 121.2, 120.7, 120.1, 104.9, 54.3, 54.1, 53.7, 50.7, 50.3, 47.0, 46.9, 46.1, 23.4, 21.7, 21.2, 20.4, 14.0, 11.3 and 11.0.

Example 17

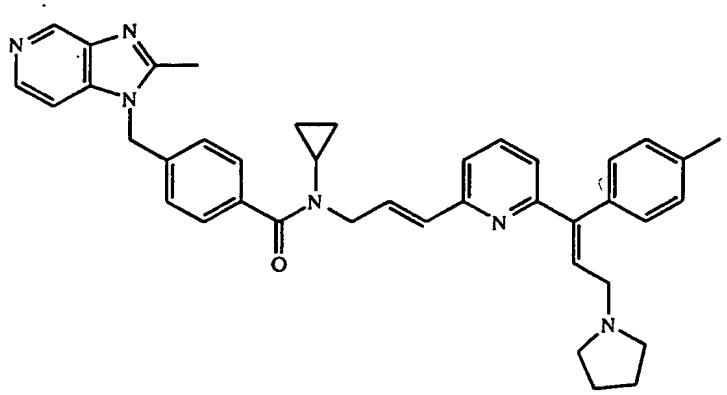
N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-propyl}-benzamide.



A solution of N-cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide (300mg, 0.45mmol) in methanol (15ml) was stirred vigorously in the presence of a palladium catalyst (30mg, 10% on charcoal) under an atmosphere of hydrogen gas for 18 hours. The catalyst was removed by filtration and solvent removed under reduced pressure. The product was purified by preparative HPLC using C-18 silica and eluting with 85% methanol, 15% 0.01M di-ammonium hydrogen phosphate buffer. Product containing fractions were combined and solvent removed. The residue was taken up in DCM and washed with saturated sodium bicarbonate solution and water. The organic layer was dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide N-cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-propyl}-benzamide as an off-white foam (58mg, 19%). ^{1}H -NMR; δ ($CDCl_3$), 9.03 (1H, s), 8.37 (1H, bs), 7.44-7.38 (4H, m), 7.34-7.02 (8H, m), 6.66 (1H, d, J=7.8Hz), 5.35 (2H, s), 3.48-3.28 (2H, bm), 3.18 (2H, d, J=7.0Hz), 2.93-2.83 (1H, bm), 2.63-0.88 (14H, m), 2.60 (3H, s), 2.58-2.52 (4H, bm), 2.39 (3H, s) and 1.80-1.74 (4H, bm); ^{13}C-NMR; δ ($CDCl_3$), 147.0, 135.6, 133.7, 130.3, 129.9, 129.1, 123.2, 122.9, 122.5, 120.6, 119.9, 114.4, 113.1, 98.4, 52.5, 48.2, 47.6, 40.6, 35.2, 29.6, 25.2, 22.4, 19.2, 18.5, 17.0, 14.8 and 7.6.

Example 18

N-Cyclopropyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Cyclopropyl)-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (241mg,0.73 mmol) in DCM (15ml) was treated with powdered 3Å molecular sieves (2g) and cyclopropylamine (100µl, 1.44mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (10ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (30mg, 0.73mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield cyclopropyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a pale brown oil (228mg, 84%). ^{1}H -NMR; δ ($CDCl_3$), 7.39 (1H, t, J=7.7Hz), 7.22-7.17 (3H, m), 7.10-7.03 (3H,

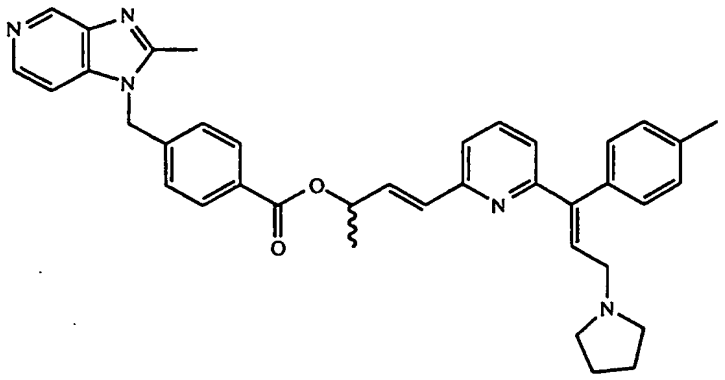
m), 6.93 (1H, dt, J=15.6, 6.2Hz), 6.66 (1H, d, J=15.6Hz), 6.60 (1H, d, J=15.6Hz), 3.52 (2H, d, J=5.8Hz), 3.17 (2H, d, J=6.9Hz), 2.56-2.47 (4H, m), 2.38 (3H, s), 2.28-2.20 (1H, m), 1.78-1.71 (4H, m), 0.50-0.36 (4H, m).

(b) N-Cyclopropyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of cyclopropyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (228mg, 0.61mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (212mg, 0.73mmol), EDC (175mg, 0.92mmol) and HOAt (10mg) in DMF (15ml) was stirred at room temperature for 120 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-25% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-cyclopropyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown foam (174mg, 46%). ^{1}H -NMR; δ ($CDCl_3$), 9.00 (1H, s), 8.34 (1H, d, J=5.5Hz), 7.54 (2H, d, J=7.8Hz), 7.44 (1H, t, J=7.8Hz), 7.30-7.13 (5H, m), 7.08 (2H, d, J=7.8Hz), 7.05 (2H, d, J=7.8Hz), 6.98-6.85 (1H, m), 6.70 (1H, d, J=7.8Hz), 6.70-6.62 (1H, m), 5.35 (2H, s), 4.33 (2H, bs), 3.51 (2H, d, J=7.2Hz), 3.00-2.88 (5H, bm), 2.57 (3H, s), 2.38 (3H, s), 1.97-1.90 (4H, m) and 0.70-0.45 (4H, bm); ^{13}C-NMR; δ ($CDCl_3$), 155.9, 154.1, 153.3, 145.2, 141.8, 141.6, 140.1, 139.6, 137.5, 137.1, 136.1, 133.9, 131.7, 130.0, 129.2, 129.1, 128.0, 125.8, 123.4, 121.0, 120.4, 105.7, 53.0, 46.9, 23.2, 21.0, 13.9 and 9.8.

Example 19

(R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]but-3E-en-2-yl ester.



(a) 4-(6-[3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-but-3E-en-2-ol.

A stirred solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (1.41g, 4.24 mmol) in anhydrous THF (50ml) at -78°C was treated dropwise with a solution of methyl magnesium bromide (1.56ml, 3.0M in diethylether, 4.67mmol). The reaction mixture was allowed to warm slowly to room temperature (~2 hours). The reaction was quenched with water (3ml) and THF removed under reduced pressure. The residue was taken up in 1M HCl and then basified with solid sodium bicarbonate to pH 8. The product was extracted with ethyl acetate (x3). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography eluting with 5% methanol in DCM. Product containing fractions were combined and solvent removed to provide 4-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-but-3E-en-2-ol as a pale brown foam (544mg, 37%). ^{1}H -NMR; δ ($CDCl_3$), 7.43 (1H, t, J=7.8Hz), 7.24-7.18 (3H, m), 7.11-7.06 (3H, m), 6.94 (1H, dd, J=15.6 and 5.8Hz), 6.71-6.64 (2H, m), 4.60-4.55 (1H, m), 3.23 (2H, d, J=7.0Hz), 2.58 (4H, bs), 2.41 (3H, s), 1.82-1.77 (4H, m), 1.41 (3H, d, J=6.5Hz).

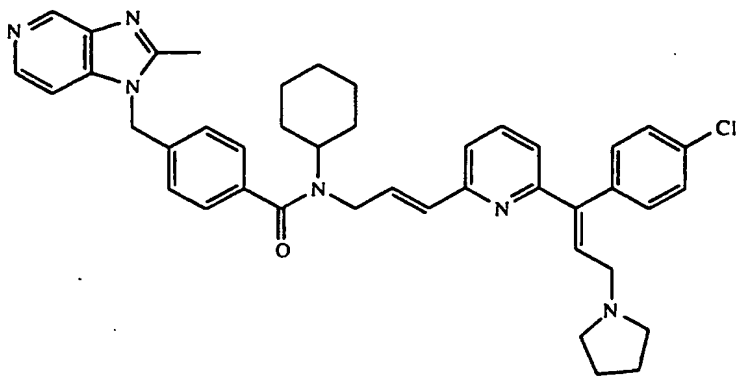
(b) (R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 4-[6-(3-

pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]but-3E-en-2-yl ester.

A solution of 4-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-but-3-en-2E-ol (510mg, 1.46mmol) in DCM (15ml) was treated with 4-(1H-2-methylimidazo [4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (466mg, 1.61mmol), EDC (420mg, 2.19mmol) and DMAP (20mg). The reaction mixture was stirred for 96 hours at room temperature. The reaction mixture was partitioned between DCM and saturated sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography eluting with 4% methanol/DCM. Product containing fractions were combined and solvent removed to yield (R,S)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 4-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]but-3E-en-2-yl ester as an off-white foam (93mg, 11%). ^{1}H -NMR; δ ($CDCl_3$), 9.04 (1H, s), 8.38 (1H, d, J=5.6Hz), 8.08 (2H, d, J=8.3Hz), 7.43 (1H, t, J=7.8Hz), 7.25-7.06 (9H, m), 6.96 (1H, dd, J=6.2, 15.6Hz), 6.71 (2H, m), 5.83 (1H, m), 5.40 (2H, s), 3.27 (2H, d, J=7.1Hz), 2.64 (4H, bs), 2.60 (3H, s), 2.40 (3H, s), 1.81 (4H, bs) and 1.56 (3H, d, J=6.6Hz); ^{13}C-NMR; δ ($CDCl_3$), 159.8, 151.9, 148.4, 148.3, 137.2, 136.8, 136.6, 135.1, 134.6, 131.9, 131.5, 129.8, 127.9, 125.8, 125.4, 124.4, 124.0, 123.5, 121.0, 116.0, 115.4, 99.6, 66.2, 49.3, 48.7, 41.9, 18.2, 16.0, 15.2 and 6.8.

Example 20

N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-chlorophenyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) 3-(6-[3-Pyrrolidin-1-yl-1-{4-chlorophenyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal.

(3-(6-[3-Pyrrolidin-1-yl-1-{4-chlorophenyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal was prepared using chemistry similar to that used to prepare 3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (example 3a). ^{1}H -NMR; δ ($CDCl_3$), 9.79 (1H, dd, J=7.8, 2.0Hz), 7.75 (1H, t, J=7.7Hz), 7.70-7.34 (4H, m), 7.25-7.09 (4H, m), 6.94 (1H, d, J=7.8Hz), 3.17 (2H, d, J=7.0Hz), 2.52 (4H, bs), 1.83-1.72 (4H, m).

(b) Cyclohexyl-{3-(6-[3-pyrrolidino-1-{4-chlorophenyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-chlorophenyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (252mg, 0.69mmol) in DCM (15ml) was treated with activated powdered 3Å molecular sieves (2g) and cyclohexylamine (75mg, 0.76mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (10ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (25mg, 6.55mmol). The reaction was stirred for 2.5 hours and solvent

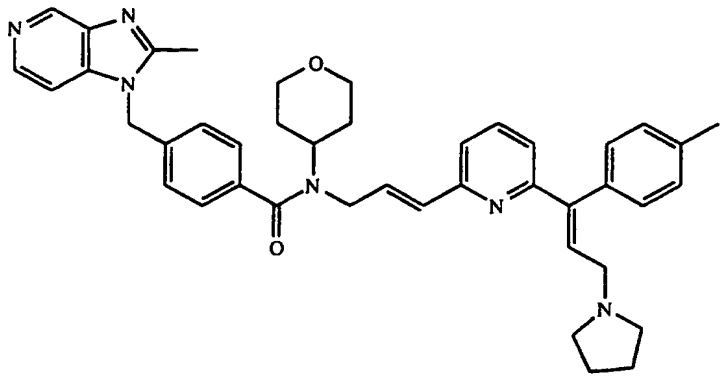
removed under reduced pressure. The residue was taken up in DCM (10ml) and washed with brine. The organics were dried over magnesium sulphate, filtered and concentrated to yield cyclohexyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-chlorophenyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a yellow oil (280mg, 96%). ^{1}H -NMR; δ ($CDCl_3$), 7.70-7.34 (3H, m), 7.22-7.09 (4H, m), 6.99-6.84 (1H, m), 6.70-6.59 (2H, m), 3.52 (2H, dd, J=6.0 and 1.0 Hz), 3.25 (1H, m), 3.16 (2H, d, J=7.0Hz), 2.54 (4H, bs), 1.97-1.93 (2H, m), 1.80-1.75 (5H, m), 1.74-1.72 (1H, m), 1.30-1.18 (6H, m).

(c) N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-chlorophenyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

A solution of cyclohexyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-p-chlorophenyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (280mg, 0.66mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (231mg, 0.80mmol), EDC (153mg, 0.80mmol) and HOAt (20mg) in DMF (15ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 5-20% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-chlorophenyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a white foam (190mg, 42%). ^{1}H -NMR; δ ($CDCl_3$), 8.97 (1H, s), 8.31 (1H, d, J=5.2Hz), 7.42 (1H, t, J=7.8Hz), 7.37-7.32 (4H, m), 7.15-7.04 (6H, m), 6.72-6.30 (3H, m), 5.25 (2H, s), 4.34-4.19 (2H, m), 2.84-2.55 (3H, m), 3.41-3.38 (3H, m), 2.84 (4H, bs), 2.55 (3H, s) 1.86-1.50 (10H, m) and 0.99 (2H, m); ^{13}C-NMR; δ ($CDCl_3$), 153.6, 142.1, 140.4, 139.9, 136.9, 136.0, 135.8, 134.0, 132.4, 131.8, 131.2, 131.0, 129.0, 127.3, 126.5, 126.2, 120.8, 120.4, 104.9, 59.1, 54.8, 53.5, 47.1, 43.2, 31.9, 30.8, 25.9, 25.7, 25.0, 23.4 and 14.1.

Example 21

N-4-Tetrahydropyranyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) 4-Amino-tetrahydropyran

A mixture of tetrahydropyranone (1.0g, 10.0mmol), ammonium acetate (7.69g, 100.0mmol), 3Å molecular sieve powder (2.5g) and sodium cyanoborohydride (1.25g, 20.0mmol) suspended in dry methanol (50ml) under a blanket of argon was refluxed for 2 hours and allowed to cool to room temperature. The suspension was filtered and concentrated under reduced pressure. The residue was partitioned between DCM and water. The organic layer was extracted with 1M HCl (x2). The combined extracts were basified with 5M sodium hydroxide solution and extracted with DCM. The combined organics were dried over magnesium sulphate, filtered and concentrated under reduced pressure to yield 4-amino-tetrahydropyran as a colourless oil (120mg, 12%). ^{1}H -NMR; δ ($CDCl_3$), 3.95-3.86 (2H, m), 3.38-3.27 (2H, m), 2.85-2.73 (1H, m), 1.79-1.67 (2H, m), 1.40-1.24 (2H, m).

(b) 4-Tetrahydropyranyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (400mg, 1.20mmol) in DCM (20ml) was treated with powdered 3Å molecular sieves (3g) and 4-amino-tetrahydropyran (200mg, 2.0mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (45mg, 1.19mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield an impure mixture containing 4-tetrahydropyranyl)-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil which was used without purification in the coupling step 21(c).

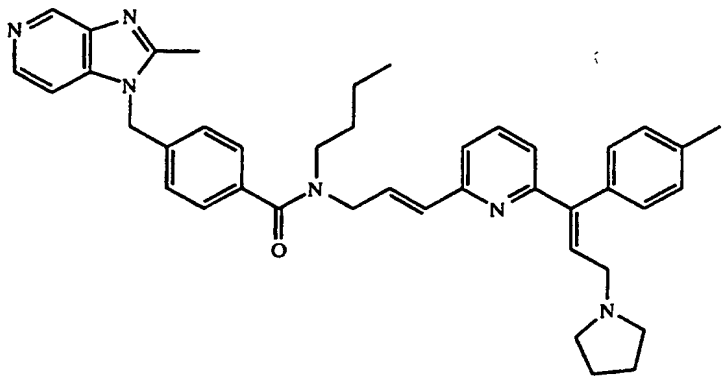
(c) N-4-Tetrahydropyranyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

A solution of 4-tetrahydropyranyl)-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (crude), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)}benzoic acid sodium salt (382mg, 1.32mmol), EDC (345mg, 1.80mmol) and HOAt (8mg) in DMF (10ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10-25% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-4-tetrahydropyranyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide as a brown foam (145mg, 16%). ^{1}H -NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.37 (1H, s), 7.43 (1H, t, J=7.8Hz), 7.40 (2H, bs), 7.22-6.39 (8H, bm), 7.21 (2H, d, J=7.9Hz), 7.07 (2H, d, J=7.9Hz), 5.36 (2H, bs), 4.70-3.14 (9H, bm), 2.66 (4H, bs), 2.59 (3H, bs), 2.39 (3H, s), 2.00-1.88 (2H, m), 1.82 (4H, bs) and 1.81-1.59 (2H, m); ^{13}C-NMR; δ ($CDCl_3$), 153.5,

148.1, 142.1, 142.0, 140.3, 139.8, 137.2, 136.8, 136.2, 134.9, 131.4, 129.6, 129.2, 127.3, 126.3, 121.1, 120.1, 104.8, 67.5, 54.5, 53.9, 47.0, 23.4, 21.2 and 14.0.

Example 22

N-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Butyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of (E)-3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (458mg, 1.38mmol) in DCM (20ml) was treated with anhydrous magnesium sulphate (2g) and butylamine (150µl, 1.52mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (53mg, 1.39mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield butyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (517mg, 96%). ^{1}H -

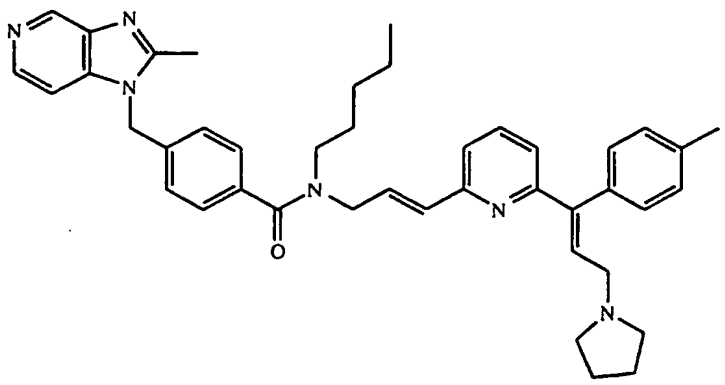
NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.8Hz), 7.23-7.17 (6H, m), 6.98-6.87 (1H, m), 6.70-6.60 (2H, m), 3.48 (2H, dd, J=6.0 and 1.2Hz), 3.19 (2H, d, J=7.0Hz), 2.69 (2H, t, J=7.0Hz), 2.54 (4H, bs), 2.41 (3H, s), 1.80-1.75 (4H, m), 1.59-1.45 (2H, m), 1.42-1.26 (2H, m), 0.94 (3H, t, J=7.2Hz).

(b) N-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

A solution of butyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (502mg, 1.29mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (411mg, 1.42mmol), EDC (372mg, 1.94mmol) and HOAt (20mg) in DMF (15ml) was stirred at room temperature for 48 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over sodium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 5-10% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as an orange foam (413mg, 50%). ^{1}H -NMR; δ ($CDCl_3$), 9.03 (1H, s), 8.38 (1H, d, J=5.6Hz), 7.45 (3H, m), 7.24-7.04 (9H, m), 6.74 (3H, bm), 5.36 (2H, s), 4.35 (0.8H, bs), 4.04 (1.2H, s), 3.56 (2H, m), 3.28 (2H, d, J=7.0Hz), 2.62 (7H, m), 2.40 (3H, s), 1.82 (4H, bs) and 1.66-0.76 (7H, bm); ^{13}C-NMR; δ ($CDCl_3$), 170.9, 157.1, 153.5, 153.3, 142.7, 142.0, 141.9, 140.3, 139.8, 137.2, 136.9, 136.3, 134.9, 132.8, 131.5, 129.6, 129.2, 127.5, 126.3, 121.2, 120.5, 120.0, 104.9, 54.5, 53.9, 50.7, 48.4, 47.0, 46.1, 45.0, 30.5, 29.3, 23.4, 21.3, 20.2, 19.7, 14.0, 13.9 and 13.6.

Example 23

N-Pentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Pentyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (1.11g, 3.34mmol) in DCM (50ml) was treated with anhydrous magnesium sulphate (5g) and pentylamine (465µl, 4.01mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a brown oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (133mg, 3.51mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over sodium sulphate, filtered and concentrated under reduced pressure to yield pentyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (1.38g, 94%). The amine was used directly in the coupling reaction 23(b).

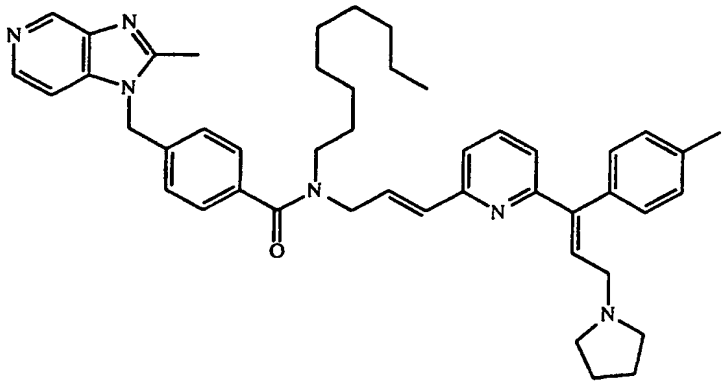
(b) N-Pentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of pentyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (1.28g, 3.17mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-

ylmethyl)benzoic acid sodium salt (1.26g, 3.45mmol), EDC (911mg, 4.76mmol) and HOAt (10mg) in DMF (15ml) was stirred at room temperature for 120 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown gum. The product was purified by column chromatography on silica-gel eluting with 10% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-pentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown foam (589mg, 28%). ^{1}H-NMR; δ (MeOD), 9.00 (1H, s), 8.35 (1H, d, J=5.5Hz), 7.45 (3H, m), 7.11 (9H, m), 6.56 (3H, m), 5.33 (2H, s), 4.33 (0.8H, m), 4.02 (1.2H, m), 3.51 (0.8H, m), 6.23 (3.2H, m), 2.57 (7H, s), 2.37 (3H, s), 1.77 (4H, m) and 1.20 (9H, m); ^{13}C-NMR; δ (MeOD), 169.3, 154.8, 152.8, 150.8, 140.5, 138.4, 138.2, 137.2, 136.6, 134.7, 134.4, 133.7, 132.3, 129.5, 126.8, 126.3, 125.2, 124.7, 124.5, 124.2, 117.5, 117.4, 116.3, 103.5, 51.5, 50.9, 48.3, 46.4, 42.8, 26.3, 25.7, 25.2, 24.0, 20.2, 19.5, 19.0, 17.4, 10.4 and 9.9.

Example 24

N-Nonyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Nonyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (319mg, 0.96mmol) in DCM (15ml) was treated with powdered 3Å molecular sieves (1.5g) and nonylamine (211µl, 1.15mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a yellow oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (36mg, 0.95mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield nonyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (462mg, contaminated with excess nonylamine). ^{1}H -NMR; δ ($CDCl_3$), 7.42 (1H, t, J=7.7Hz), 7.23-7.17 (3H, m), 7.13-7.06 (3H, m), 6.93 (1H, dt, J=15.8, 6.1Hz), 6.68 (1H, d, J=7.9Hz), 6.63 (1H, d, J=15.8Hz), 3.48 (2H, dd, J=6.1, 1.4Hz), 3.19 (2H, d, J=7.1Hz), 2.68 (2H, t, J=7.2Hz), 2.57-2.49 (4H, m), 2.41 (3H, m), 1.81-1.75 (4H, m), 1.58-1.46 (2H, m), 1.36-1.22 (13H, m) and 0.89 (3H, t, J=6.9Hz).

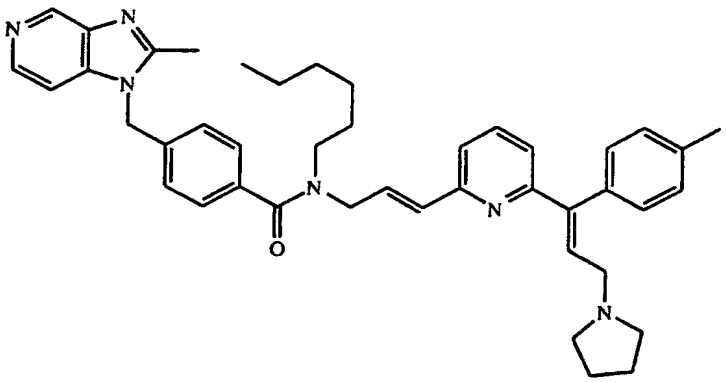
(b) N-Nonyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of nonyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (462mg, 1.0mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (349mg, 1.2mmol), EDC (288mg, 1.5mmol) and HOAt (10mg) in DMF (10ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 15-25% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-nonyl-4-

(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown foam (386mg, 54%). ^{1}H -NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.36 (1H, d, J=5.5Hz), 7.47-7.40 (3H, m), 7.25-6.97 (9H, m), 6.88-6.44 (3H, m), 5.35 (2H, s), 4.40-4.26 (0.8H, m), 4.08-3.99 (1.2H, m), 3.67-3.48 (1.2H, m), 3.31 (2H, d, J=7.0Hz), 3.30-3.18 (0.8H, m), 2.76-2.60 (4H, bm), 2.58 (3H, s), 2.39 (3H, s), 1.89-1.76 (4H, bm), 1.72-1.04 (14H, m) and 0.85 (3H, t, J=6.6Hz); ^{13}C-NMR; δ ($CDCl_3$), 170.8, 157.0, 153.4, 142.9, 142.0, 141.9, 140.3, 139.8, 137.2, 136.9, 136.7, 136.2, 134.9, 132.7, 131.4, 129.6, 129.2, 127.5, 126.2, 121.2, 120.5, 119.9, 104.8, 54.4, 53.8, 50.6, 48.6, 47.0, 46.0, 45.2, 31.7, 29.3, 29.1, 28.4, 27.1, 26.9, 26.4, 23.4, 22.6, 21.2 and 14.0.

Example 25

N-Hexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) Hexyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (1.11g, 3.34mmol) in DCM (50ml) was treated with magnesium sulphate (5g) and hexylamine (465µl, 4.01mmol). The reaction was stirred for 18 hours, filtered and concentrated under reduced pressure to provide the imine as a green oil. The residue was resuspended in dry methanol (15ml), cooled in an ice-salt bath and treated under an inert atmosphere with sodium borohydride (131mg, 3.47mmol). The reaction was stirred for 2 hours and solvent removed under reduced pressure. The residue was taken up in DCM and washed with saturated sodium bicarbonate. The organics were dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield hexyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine as a brown oil (1.37g, ~100%). The amine was used directly in the coupling reaction 25(b).

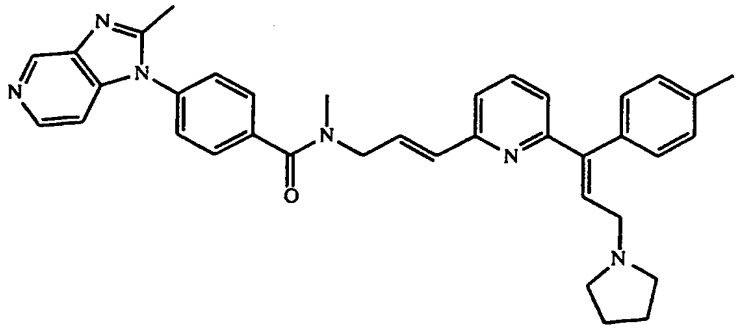
(b) N-Hexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide.

A solution of hexyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (1.37g, 3.30mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (1.31g, 3.63mmol), EDC (949mg, 4.95mmol) and HOAt (10mg) in DMF (15ml) was stirred at room temperature for 168 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 20% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-hexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a brown foam (699mg, 32%). ^{1}H-NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.36 (1H, d, J=5.3Hz), 7.41 (3H, m), 7.19 (4H, m), 7.06 (5H, m), 6.75 (2.5H, m), 6.70 (0.5H, d, J=8.0Hz), 5.34 (2H, bs), 4.34 (0.8H, bd, J=4.7Hz), 4.01 (1.2H, bd, J=2.7Hz), 3.52 (0.8H, bt, J=7.3Hz), 3.21 (1.2H, m), 3.17 (2H,

d, J=6.9Hz), 2.58 (3H, s), 2.51 (4H, m), 2.38 (3H, s), 1.75 (4H, m), 1.65 (1.2H, m), 1.51 (0.8H, m), 1.20 (6H, m) and 0.85 (3H, m); ^{13}C-NMR; δ ($CDCl_3$), 170.8, 157.5, 153.5, 153.2, 142.1, 142.0, 141.4, 140.3, 139.8, 136.9, 136.9, 136.6, 136.2, 135.4, 135.3, 133.0, 131.6, 130.7, 129.7, 129.3, 129.1, 127.6, 127.5, 126.2, 121.1, 120.9, 120.3, 119.7, 54.8, 54.2, 50.2, 48.5, 47.0, 46.0, 45.0, 31.6, 31.1, 28.3, 27.1, 26.6, 26.1, 23.5, 22.6, 22.4, 21.3 and 14.0.

Example 26

N-Methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

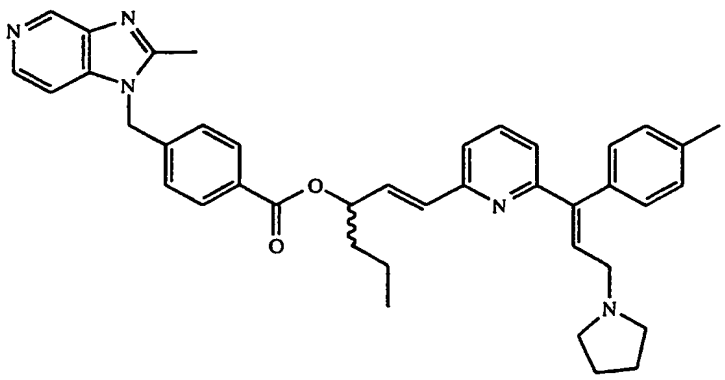


A suspension of 4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)benzoic acid (WO 9214734, 500mg, 1.98mmol) in DCM (15ml) was treated with EDC (380mg, 1.98mmol) and HOBt (270mg, 1.98mmol). The reaction was stirred at room temperature for 3 hours. The reaction mixture was partitioned between DCM and brine. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under vacuum to a colourless oil. The oil was taken up in DMF (10ml), treated with a solution of methyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (250mg, 0.72mmol) also in DMF (2ml) and stirred

at 40°C for 18 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were separated, washed with brine, dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown oil. The product was purified by column chromatography on silica-gel eluting with 10-14% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide as a white solid (45mg, 11%). ^{1}H -NMR; δ ($CDCl_3$), 9.02 (1H, bs), 8.36 (1H, bs), 7.77 (2H, d, J=6.7Hz), 7.46-7.37 (3H, m), 7.24-7.21 (3H, m), 7.10-6.90 (5H, m), 6.74-6.59 (2H, m), 4.43 (1H, bs), 4.20 (1H, bs), 3.60 (2H, bs), 3.16 and 3.14 (3H, 2xs), 3.04 (4H, bs), 2.55 (3H, s), 2.39 (3H, s) and 1.98 (4H, bs); ^{13}C-NMR; δ ($CDCl_3$),170.6, 155.8, 154.1, 152.9, 142.4, 141.7, 140.8, 139.7, 138.0, 137.1, 136.9, 136.0, 133.6, 132.7, 131.3, 129.5, 129.2, 128.7, 126.7, 121.6, 121.3, 120.7, 105.2, 53.7, 53.4, 53.1, 49.1, 37.4, 33.4, 23.2, 21.1 and 14.4.

Example 27

(R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid (E)-1-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]hex-1-en-3-yl ester.



(a) 1-(6-[3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-hex-1E-en-3-ol.

A stirred solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enal (925mg, 2.78 mmol) in anhydrous THF (30ml) at -78°C was treated dropwise with a solution of n-propyl magnesium chloride (1.53ml, 2.0M in diethylether, 3.06mmol). The reaction mixture was allowed to warm slowly to room temperature (~2 hours). The reaction was quenched with water (3ml) and THF removed under reduced pressure. The residue was taken up in 1M HCl and then basified with solid sodium bicarbonate to pH 8. The product was extracted with ethyl acetate (x3). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography eluting with 5-8% methanol in DCM. Product containing fractions were combined and solvent removed to provide 1-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-hex-1E-en-3-ol as a pale pink foam (593mg, 57%). ^{1}H-NMR; δ ($CDCl_3$), 7.44 (1H, t, J=7.7Hz), 7.24-7.18 (3H, m), 7.12-7.07 (3H, m), 6.89 (1H, dd, J=15.7, 6.2Hz), 6.68 (2H, m), 4.38 (1H, m), 3.35 (2H, d, J=7.1Hz), 2.41 (4H, bs), 1.86 (3H, s), 1.71-1.61 (2H, m), 1.58-1.42 (2H, m), 1.47 (3H, t, J=7.0Hz).

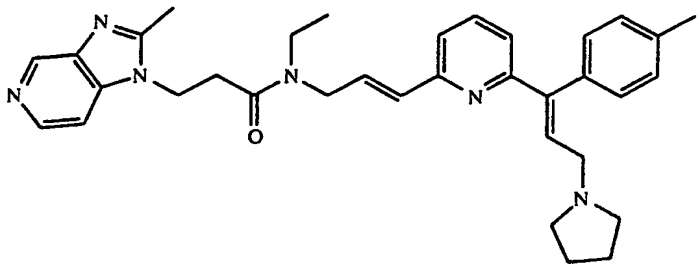
(b) (R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 1-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]hex-1E-en-3-yl ester.

A solution of 3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-hex-5E-en-4-ol (300mg, 0.80mmol) in DCM (10ml) was treated with 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (255mg, 0.88mmol), EDC (230mg, 1.20mmol) and DMAP (20mg). The reaction mixture was stirred for 96 hours at room temperature. The reaction mixture was partitioned between DCM and saturated sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure. The product was purified by column chromatography eluting with 5-15% methanol/DCM. Product containing fractions were combined and solvent removed to yield (R,S)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 1-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]hex-1E-en-3-yl ester as a brown foam (93mg, 19%). ^{1}H-NMR; δ ($CDCl_3$), 9.04 (1H, s), 8.37 (1H, d, J=5.6Hz), 8.07 (2H, d, J=8.3Hz),

7.40 (1H, t, J=7.8Hz), 7.27-7.02 (9H, bm), 6.91 (1H, dd, J=6.7, 15.6Hz), 6.68 (2H, m), 5.72 (1H, m), 5.39 (2H, s), 3.18 (2H, d, J=7.1Hz), 2.59 (3H, s), 2.52 (4H, bs), 2.39 (3H, s), 1.87 (2H, m), 1.76 (4H, bs), 1.47 (2H, m) and 0.96 (3H, t, J=7.3Hz); ^{13}C-NMR; δ ($CDCl_3$), 165.1, 157.3, 153.6, 153.4, 142.1, 142.0, 141.6, 140.3, 139.8, 139.7, 136.9, 136.6, 135.4, 132.0, 131.8, 130.7, 130.6, 130.2, 129.7, 129.1, 126.1, 121.1, 120.5, 104.7, 75.0, 54.8, 54.1, 47.1, 36.6, 23.4, 21.2, 18.5, 14.0 and 13.8.

Example 28

N-Ethyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propylamide.



(a) tert-Butyl-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propanoate.

A solution of 4-chloro-3-nitropyridine (2.94g, 18.54mmol) and β-alanine-tert-butyl ester hydrochloride (5.05g, 27.8mmol) in DMF (30ml) was treated with triethylamine (6.5ml, 46.4mmol) and stirred at room temperature for 50 hours. The solvent was removed under reduced pressure and residue partitioned between DCM and water. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated under reduced pressure to a dark oil. The residue was dissolved in methanol (50ml), treated with palladium catalyst (500mg, 10% on charcoal) and stirred under an atmosphere of hydrogen gas for 24 hours. The catalyst was removed by filtration and solvent removed under reduced pressure. The residue was

dissolved in a mixture of acetic acid (50ml) and acetic anhydride (50ml). The resulting solution was heated at 140°C for 28 hours, cooled and concentrated under reduced pressure. The product was purified by column chromatography eluting with 7% methanol in DCM. Product containing fractions were combined and solvent removed to yield tert-butyl-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propanoate as a pale yellow oil (1.54g, 32%). ^{1}H -NMR; δ ($CDCl_3$), 8.98 (1H, s), 8.42 (1H, d, J=6.9Hz), 7.38 (1H, d, J=6.7Hz), 4.41 (2H, t, J=6.8Hz), 2.73 (2H, t, J=6.7Hz), 2.70 (3H, s), 1.35 (9H, s).

(b) 3-(1H-2-Methylimidazo[4,5-c]pyridin-1-yl)-propanoic acid.

A solution of tert-butyl-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propanoate (1.54g, 5.9mmol) in trifluoroacetic acid (50ml) was allowed to stand at room temperature overnight. The reaction mixture was concentrated under reduced pressure to a brown gum. Addition of ethyl acetate gave 3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propanoic acid as a brown solid which was collected by filtration (1.08g, 89%). ^{1}H-NMR; δ (MeOD), 9.15 (1H, s), 8.56 (1H, d, J=6.8Hz), 8.27 (1H, d, J=6.9Hz), 4.70 (2H, t, J=7.2Hz), 2.98 (2H, t, J=7.3Hz), 2.84 (3H, s).

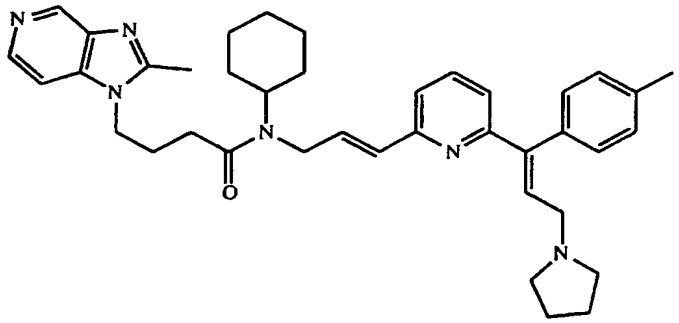
(c) N-Ethyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propylamide.

A solution of ethyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (380mg, 1.05mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)propanoic acid (180mg, 0.86mmol), EDC (247mg, 1.29mmol) and HOAt (10mg) in DMF (15ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 10% methanol and 1% triethylamine in DCM. Product containing fractions were combined and solvent removed to yield N-ethyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-3-

(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propylamide (91mg, 17%). ^{1}H-NMR; δ (MeOD), 8.68 (0.5H, s), 8.56 (0.5H, s), 8.20 (0.5H, d, J=5.9Hz), 7.98 (0.5H, d, J=5.5Hz), 7.61 (0.5H, d, J=5.9Hz), 7.45 (1.5H, m), 7.17 (2H, d, J=8.0Hz), 7.07 (0.5H, d, J=7.2Hz), 7.00 (2H, m), 6.90 (1.5H, m), 6.73 (1H, t, J=6.1Hz), 6.51 (1H, m), 6.36 (0.4H, d, J=15.9Hz), 6.12 (0.6H, d, J=15.8Hz), 4.48 (2H, m), 4.02 (2H, m), 3.52 (2H, m), 3.24 (2H, m), 2.93 (6H, m), 2.64 (1.1H, s), 2.60 (1.9H, s), 2.28 (3H, s), 1.82 (4H, m) and 0.95 (3H, m); ^{13}C-NMR; δ (MeOD), 171.8, 171.5, 158.1, 157.9, 157.0, 157.0, 155.1, 147.1, 147.0, 142.0, 141.8, 141.5, 140.8, 140.7, 139.1, 138.4, 135.6, 132.8, 131.7, 131.2, 130.9, 130.7, 130.5, 124.8, 124.6, 122.6, 122.5, 121.7, 107.7, 54.8, 54.8, 54.6, 50.1, 48.0, 43.6, 42.8, 41.6, 41.5, 33.2, 33.0, 30.7, 24.1, 21.3, 14.2, 13.8 and 13.1.

Example 29

N-Cyclohexyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butylamide.



(a) Ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butanoate.

Using procedures similar to those described in example 28(a) ethyl-4-aminobutyrate (3.0g, 17.9mmol) was used to prepare ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butanoate (688mg, 75%). ^{1}H -NMR; δ ($CDCl_3$), 8.98 (1H, s), 8.39 (1H, d, J=5.5Hz), 7.28 (1H, d, J=5.6Hz), 4.15 (4H, m), 2.65 (3H, s), 2.37 (2H, t, J=6.9Hz), 2.11 (2H, m), 1.25 (3H, t, J=7.3Hz).

(b) 4-(1H-2-Methylimidazo[4,5-c]pyridin-1-yl)-butanoic acid sodium salt.

A solution of ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butanoate (688mg, 2.93mmol) in a mixture of THF and water (4:1, 10ml) was treated with an aqueous solution of sodium hydroxide (3.04ml of a 1.01M solution, 3.07mmol). The reaction was warmed at 40°C for 18 hours and solvent removed under reduced pressure to yield 4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butanoic acid sodium salt as a pale yellow solid (680mg, 96%). ^{1}H -NMR; δ (MeOD), 8.67 (1H, d, J=0.9Hz), 8.19 (1H, d, J=5.8Hz), 7.56 (1H, dd, J=5.5, 0.9Hz), 4.20 (2H, t, J=7.4Hz), 2.58 (3H, s), 2.11 (2H, t), 1.96 (2H, s).

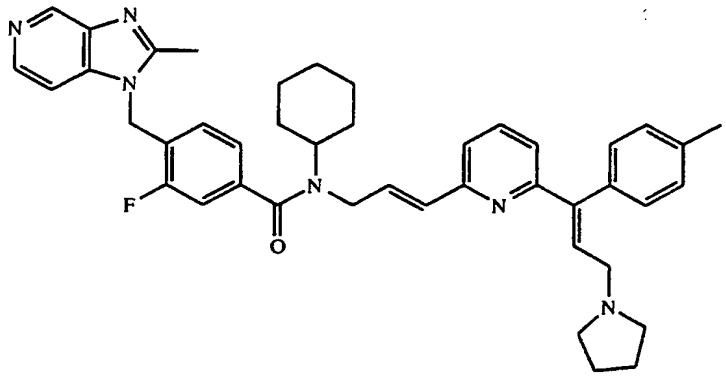
(c) N-Cyclohexyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butylamide.

A solution of cyclohexyl-{3-(6-[3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (990mg, 2.37mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)}-butanoic acid sodium salt (680mg, 2.82mmol), EDC (681mg, 3.60mmol) and HOAt (10mg) in DMF (15ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 5% methanol and 1% triethylamine in DCM. Product containing fractions were combined and solvent removed to yield N-cyclohexyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butylamide as an off-white foam (279mg, 19%). ^{1}H -NMR; δ ($CDCl_3$), 8.67 (0.5H, s), 8.61 (0.5H, s), 8.15 (0.5H, d, J=5.7Hz), 8.11 (0.5H, d, J=5.7Hz), 7.43 (2H, m), 7.10 (3H, m), 6.94 (2H, d, J=8.1Hz), 6.85 (0.5H, t, J=6.9Hz), 6.60 (3.5H, m), 4.26 (1H, t, J=7.3Hz), 4.17 (1H, t, J=7.4Hz), 4.01 (2H, m), 3.13 (2H, m), 2.51 (8H, m), 2.25 (3H, s), 2.01 (2H, m) and 1.50 (16H, m); ^{13}C-NMR; δ (MeOD), 170.2, 169.2, 154.8, 152.7, 152.5, 152.1,

151.2, 140.4, 140.3, 138.0, 137.9, 136.9, 136.4, 134.6, 134.4, 134.2, 132.4, 129.1, 129.0, 128.3, 126.8, 126.2, 125.4, 125.1, 118.2, 118.1, 117.3, 117.0, 103.4, 103.3, 54.6, 51.5, 50.8, 42.0, 40.5, 40.4, 40.4, 40.1, 28.7, 27.6, 27.3, 26.8, 26.4, 23.1, 22.9, 22.3, 22.0, 21.9, 21.2, 9.7 and 9.6.

Example 30

N-Cyclohexyl-3-fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) 3-Fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt.

3-Fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt was prepared using chemistry similar to that reported in the literature for 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt. ^{1}H -NMR; δ (MeOD), 8.71 (1H, d. J=0.79Hz), 8.18 (1H, d, J=5.8Hz), 7.62-7.53 (2H, m), 7.43 (1H, d, J=5.5Hz), 6.97 (1H, t, J=7.7Hz), 5.49 (2H, s), 2.56 (3H, s).

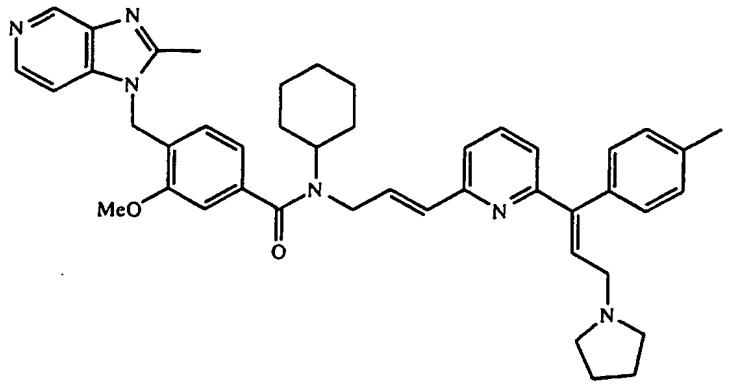
(b) N-Cyclohexyl-3-fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-

(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

A solution of cyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2-enyl}-amine (1.13g, 2.72mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (920mg, 3.00mmol), EDC (780mg, 4.08mmol) and HOAt (370mg, 2.72mmol) in DMF (15ml) was stirred at room temperature for 96 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The product was purified by column chromatography on silica-gel eluting with 5-15% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-cyclohexyl-3-fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a pale brown foam (747mg, 40%). ^{1}H-NMR; δ ($CDCl_3$), 9.03 (1H, s), 8.39 (1H, d, J=5.6Hz), 7.43 (1H, t, J=7.8Hz), 7.27-7.07 (9H, m), 6.78 (4H, m), 5.39 (2H, s), 4.23 (2.3H, m), 3.98 (0.7H, m), 3.26 (2H, d, J=6.7Hz), 2.64 (7H, bs), 2.40 (3H, s), 1.80 (4H, bs) and 1.62-1.06 (10H, bm); ^{13}C-NMR; δ ($CDCl_3$), 161.8, 157.8, 157.1, 153.4, 142.0, 141.9, 140.1, 139.7, 136.9, 136.5, 135.0, 131.8, 131.3, 130.6, 129.6, 129.0, 128.2, 123.2, 123.0, 122.6, 120.8, 119.7, 114.5, 114.1, 104.7, 59.1, 54.9, 54.4, 53.8, 50.4, 47.2, 43.2, 41.3, 41.2, 31.8, 30.6, 25.6, 24.9, 23.4 and 13.8.

Example 31

N-Cyclohexyl-3-methoxy-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.



(a) 3-Methoxy-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt.

3-Methoxy-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt was prepared using chemistry similar to that reported in the literature for 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt. ^{1}H -NMR; δ (MeOD), 7.99 (1H, d, J=0.8Hz), 7.45 (1H, d, J=5.8Hz), 6.80 (1H, d, J=1.3Hz), 6.73-6.67 (2H, m), 6.19 (1H, d, J=7.8Hz), 4.06 (3H, s), 3.03 (3H, s).

(b) N-Cyclohexyl-3-methoxy-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide.

A solution of cyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine (1.05g, 2.53mmol), 4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid sodium salt (890mg, 2.78mmol), EDC (730mg, 3.80mmol) and HOAt (340mg, 2.53mmol) in DMF (15ml) was stirred at room temperature for 48 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and brine. The organics were dried over magnesium sulphate, filtered and solvent removed under reduced pressure to leave a brown foam. The

product was purified by column chromatography on silica-gel eluting with 5-15% methanol in DCM. Product containing fractions were combined and solvent removed to yield N-cyclohexyl-3-fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-benzamide as a pale brown foam (646mg, 37%). ^{1}H-NMR; δ ($CDCl_3$), 9.00 (1H, s), 8.34 (1H, d, J=5.5Hz), 7.42 (1H, t, J=7.8Hz), 7.22 -6.70 (13H, m), 5.31 (2H, bs), 4.23-3.56 (6H, bm), 3.30 (2H, d, J=6.2Hz), 2.67 (4H, bs), 2.60 (3H, s), 2.39 (3H, s) and 1.82-1.06 (14H, m); 156.7, 153.9, 141.7, 140.5, 139.8, 137.2, 136.6, 134.8, 131.7, 131.2, 129.5, 129.2, 127.2, 124.0, 120.9, 119.9, 118.3, 109.1, 105.1, 55.5, 54.1, 53.6, 42.9, 32.0, 25.7, 23.4, 21.1 and 13.9.

Pharmacology Example 1

Inhibition of [^{3}H]-Pyrilamine Binding to Histamine-1 Receptors on Hela-S3 Cells

The inhibition of [^{3}H]-pyrilamine binding to histamine-1 receptors on Hela-S3 cells (American Type Culture Collection) was determined by isotopic labelling and filtration techniques. A suspension of the cells in buffer (25ml, 0.5% Bovine Serum Albumin, 0.1% sodium azide, phosphate buffered saline (PBS)) was centrifuged at 1000 rpm for 5 minutes in a JOUAN CR 422 centrifuge, collected, resuspended in buffer (25ml) and spun again. The cells were counted using a haemocytometer and resuspended in buffer to provide a final concentration of 4.5 x 10^6 cells ml^{-1}. A portion of the Hela-S3 cell suspension (1ml) was added to each assay tube containing 25µl of vehicle (50% DMSO/buffer) or 25µl of test compound solution (dissolved in DMSO and diluted with sufficient PBS to give a final test concentration of 1µM) and 25µl of [^{3}H]-pyrilamine (supplied by Amersham International and diluted with PBS to 3nM). The tubes were mixed, incubated at 37°C for 30 minutes and then spun at 4°C at 2000 rpm for 2 minutes. The supernatant was removed and the cells resuspended in buffer (repeated x2). The cells were suspended in 300µl of a 2:1 solution of 1M sodium hydroxide and 1% sodium dodecyl sulphate. The tubes were left overnight before the contents were tranferred to a scintillation vial, treated with

10ml, OPTIPHASE MP scintillation fluid (OPTIPHASE MP is a trade mark) and the radioactivity counted in a scintillation counter. Non-displacable binding (NDB) was determined using Astemizole (5×10^{-5} M) in place of test compounds. Defining the counts for total binding from the vehicle control sample as "TB" and the counts for total binding with antagonist as "TBA" the percentage specific binding (%SB) can be determined from the following equation.

$$\%SB = \frac{(TBA - NDB)}{(TB - NDB)} \times 100 \ \%$$

Results

Example	% Specific Binding at 1μM
1	16
2	15
3	19
4	42
5	16
6	29
7	40
8	34
9	63
10	62
11	60
12	64
13	30
16	30
17	58
22	31
26	26

Pharmacology Example 2

Inhibition of PAF-Induced Platelet Aggregation

Male New Zealand White rabbits (3.0 - 3.5 kg) were anaesthetised by intravenous administration of sodium pentobarbitone, 18mg.ml^{-1}, *via* a marginal ear vein. The trachea was exposed and connected to a respiratory pump (Harvard UK) to provide artificial ventilation. A carotid artery was exposed and cannulated and the animal was exsanguinated. Whole blood was collected in a syringe containing tri-sodium citrate (3.8% w/v) to a ratio of 1 part citrate : 9 parts blood.

Collected blood was centrifuged at 180 x g for 15 minutes at room temperature (21°C) to prepare platelet-rich plasma (PRP). The remaining blood was then centrifuged at 1800 x g for 10 minutes at room temperature to obtain platelet poor plasma (PPP).

Platelet count of the PRP was measured using a Technicon H1 blood cell differential analyser (Bayer Diagnostics UK) and adjusted with PPP to obtain a final platelet count of 500,000 platelets per µl of plasma, this being the normal physiological platelet count for rabbits. Corrected PRP was left to equilibrate at room temperature for 30 minutes before use.

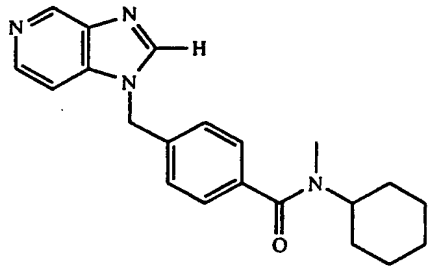
Aggregation studies were carried out using a 4-channel aggregometer (PAP-4C, BioData USA) as follows: 400 µl aliquots of PRP were placed in siliconised cuvettes and incubated to 37°C for 1 to 2 minutes in the heating block of the aggregometer. Baseline (100% aggregation) was set up using PPP (500 µl in a siliconised cuvette). The PRP was placed into a measuring well of the aggregometer, and a stirrer bar was added. The sample was stirred at 1000 rpm. The machine was activated to set the 0% aggregation level. Test compound or vehicle (50 µl) was added to the PRP, where any effects on the baseline was noted. PAF (100 ngml^{-1} as 50 µl aliqout) was added to the PRP 3 minutes after test compound or vehicle. Aggregation was measured for a further 4 minutes after PAF addition and the maximum aggregation

over the 4 minutes was recorded.

The investigation of different concentrations of test compound was performed in triplicate. Data were expressed as 0% aggregation of the sample and test compound data were compared to vehicle data to obtain % inhibition of the PAF-induced aggregation from which IC_{50} values could be determined.

PAF was made up in sterile saline (NaCl 0.9% w/v) containing BSA (0.25% w/v) from an initial stock solution (10 $mgml^{-1}$ in EtOH). Test compounds were made up as 1 x 10^{-3}M stock solutions in sterile saline containing molar equivalents of 1N HCl (v/v) or in DMSO.

In the results which follow, a comparison compound A was included. Compound A was prepared as described in EP-A-260613 (G.D. Searle), but is not part of the present invention. As appears from the results of the comparison, compounds of this invention, all of which incorporate a fragment capable of H_1 antagonist activity, are observed to show improved PAF antagonist activity over compound A.



(A)

Results

Example	PAF-Induced Platelet Aggregation IC_{50} (nM)

1	2100
2	542
3	1480
4	167
5	2200
6	333
7	133
8	92
9	43
10	2010
11	176
12	58
13	238
16	130
17	315
22	62
Compound A	74000

Pharmacology Example 3

Histamine Induced Bronchoconstriction in the Anaesthetised Guinea Pig

Following oral administration of test compound or vehicle by oral gavage, male Dunkin-Hartley guinea pigs (350-400g) were anaesthetised by intraperitoneal injection of 60mgkg^{-1} sodium pentobarbitone (Sagatal, May & Baker UK). Through a midline incision of the neck, the trachea was cannulated and connected to a small animal respirator (Harvard, UK). Animals were artificially ventilated at a rate of 30 breaths per minute with a tidal volume of 8-10ml to give a resting tracheal inflation pressure of 15mmHg as measured by a physiological pressure transducer (type P23XL, Spectramed USA) connected to a side arm of the respiratory circuit.

A jugular vein was cannulated for the administration of propranolol and for the infusion of histamine. A carotid artery was cannulated for the measurement of arterial blood pressure via a physiological pressure transducer (type P23XL, Spectramed USA). Blood pressure and tracheal inflation pressure were recorded on a thermal array chart recorder (type TA4000, Gould Electronics UK).

Following a suitable equilibration period, propranolol (1mgkg^{-1} i.v. & 3mgkg^{-1} s.c. Sigma Chemical Co. UK) was administered to inhibit any resulting catecholamine release following histamine administration.

Histamine infusion (10μgkg^{-1}min^{-1} at a rate of 10mlhr^{-1} using a perfusion pump type Perfuser securer FT, B. Braun Germany) was started at the one hour time point following oral administration of the test compound or vehicle. Changes in tracheal inflation pressure and blood pressure of drug treated animals were compared with changes from vehicle treated animals and ED_{50} values determined. One dose of test compound was investigated per animal.

Results

Example	ED_{50} mgkg^{-1}, p.o. or % inhibition
3	0.40
4	0.85
13	1.00
16	46% at 10mg/kg
20	1.00

Pharmacology Example 4

PAF Induced Bronchoconstriction in the Anaesthetised Guinea Pig

Following oral administration of test compound or vehicle, male Dunkin-Hartley guinea pigs (350-400g) were anaesthetised by intraperitoneal injection of 60mgkg^{-1} sodium pentobarbitone (Sagatal, May & Baker UK). Through a midline incision of the neck, the trachea was cannulated and connected to a small animal respirator (Harvard, UK). Animals were artificially ventilated at a rate of 30 breaths per minute with a tidal volume of 8-10ml to give a resting tracheal inflation pressure of 15mmHg as measured by a physiological pressure transducer (type P23XL, Spectramed USA) connected to a side arm of the respiratory circuit.

A jugular vein was cannulated for the administration of a bolus dose of propranolol and for the later administration of bolus PAF. A carotid artery was cannulated for the measurement of arterial blood pressure via a physiological pressure transducer (type P23XL, Spectramed USA). Blood pressure and tracheal inflation pressure were recorded on a thermal array chart recorder (type TA4000, Gould Electronics UK).

Propranolol (1mgkg^{-1} i.v. & 3mgkg^{-1} s.c. Sigma Chemical Co. UK) was administered 10 minutes before PAF in order to prevent the bronchodilatory activity of catecholamines which may be released in response to PAF administration. PAF (100ngkg^{-1} i.v. bolus) was administered at the one hour time point following oral administration of the test compound or vehicle.

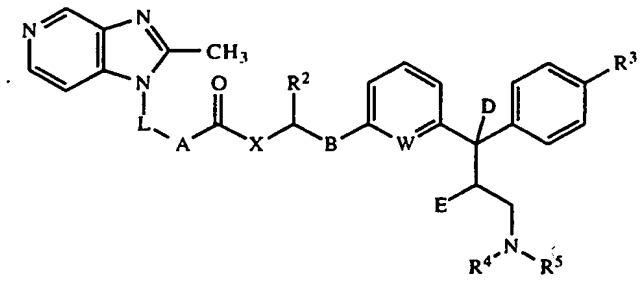
Changes in tracheal inflation pressure and blood pressure of drug treated animals were compared with changes from vehicle treated animals and percentage inhibition determined. One dose of test compound was investigated per animal.

Results

Example	ED_{50} mgkg^{-1}, p.o.
3	5.8
4	1.55
13	2.55
16	1.55
20	4.20

Claims:

1. A compound of formula (II)



(II)

wherein:

L and A are such that (i) L represents an unbranched saturated or unsaturated divalent hydrocarbon chain having up to 6 carbon atoms and A represents a bond, or (ii) L represents a bond or $-CH_2-$ and A represents a divalent 1,4-phenylene group which may be substituted by C_1-C_6 alkyl, C_2-C_6 alkenyl, cyano, halogen or C_1-C_6 alkoxy;

X represents (a) -O-; or (b) $-N(R^1)-$ wherein R^1 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl or non-aromatic 5 to 7 membered heterocyclyl, any of which which may be substituted with one or more C_1-C_6 alkyl, $-(C=O)O(C_1$-C_6 alkyl), -COOH, or phenyl groups;

R^2 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl or non-aromatic 5 to 7 membered heterocyclyl which may be substituted with one or more C_1-C_6 alkyl, $-(C=O)O(C_1$-C_6 alkyl), -COOH, or

phenyl groups;

B represents a bond, or a straight or branched saturated or unsaturated divalent hydrocarbon chain of up to 3 carbon atoms;

R^3 represents hydrogen, C_1-C_4 alkyl, halogen, cyano, trifluoromethyl or C_1-C_4 alkoxy;

W represents -N= or -C=;

D represents hydrogen or a hydroxyl and E represents hydrogen, or D and E taken together represent -C=C-;

R^4 and R^5 are independently C_1-C_6 alkyl or together with the nitrogen atom to which they are attached form a non-aromatic 5-7 membered heterocyclic ring, which may contain one or more heteroatoms other than the nitrogen to which R^3 and R^4 are attached;

or a pharmaceutically or veterinarily acceptable acid addition salt, solvate or hydrate thereof.

2. A compound as claimed in claim 1 wherein L is 1,2-ethylene or 1,3-propylene and A is a bond.

3. A compound as claimed in claim 1 wherein L is $-CH_2-$ and A is 1,4-phenylene, 3-fluoro-1,4-phenylene or 3-methoxy-1,4-phenylene.

4. A compound as claimed in any one of the preceding claims wherein X represents $-N(R^1)-$ wherein R^1 represents hydrogen, cyclopropyl, cyclopentyl, 3,5-dimethylcyclohex-1-yl, 3-methylbut-1-yl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-propyl, isopropyl, n-pentyl, n-nonyl, 2-ethylcarboxylate-3-methylbut-1-yl, benzyl, or tetrahydropyranyl.

5. A compound as claimed in any one of claims 1 to 3 wherein X represents -N(R^1)- wherein R^1 represents cyclohexyl, methyl or ethyl.

6. A compound as claimed in any one of the preceding claims wherein R^2 represents hydrogen.

7. A compound as claimed in any one of the preceding claims wherein B represents $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH=CH-$, or $-CH=CHCH_2-$.

8. A compound as claimed in any one of claims 1 to 6 wherein B represents -CH=CH- (trans).

9. A compound as claimed in any one of the preceding claims wherein R^3 represents hydrogen, C_1-C_4 alkyl, or halogen.

10. A compound as claimed in any one of claims 1 to 9 wherein R^3 represents methyl.

11. A compound as claimed in any one of the preceding claims wherein W represents -N=.

12. A compound as claimed in any one of the preceding claims wherein D and E taken together represent -C=C-;

13. A compound as claimed in any one of the preceding claims wherein R^4 and R^5 together represent a group $-(CH_2)_m-$ wherein m is 5, or 6.

14. A compound as claimed in any one of claims 1 to 12 wherein R^4 and R^5 together represent a group $-(CH_2)_m-$ wherein m is 4.

15. A compound as claimed in claim 1 wherein L is $-CH_2-$ and A is 1,4-phenylene,

3-fluoro-1,4-phenylene or 3-methoxy-1,4-phenylene; X represents -N(R^1)- wherein R^1 is cyclohexyl, methyl or ethyl; R^2 is hydrogen; B is -CH=CH- (trans); R^3 is methyl; W is -N=; D and E taken together represent -C=C-; and R^4 and R^5 together represent a group -$(CH_2)_m$- wherein m is 4, or a pharmaceutically or veterinarily acceptable acid addition salt, solvate or hydrate thereof.

16. N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-(E)-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2-enyl}-benzamide, or a pharmaceutically or veterinarily acceptable acid addition salt, solvate or hydrate thereof.

17. N-Ethyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-(E)-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2-enyl}-benzamide, or a pharmaceutically or veterinarily acceptable acid addition salt, solvate or hydrate thereof.

18. A compound selected from the group consisting of:

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]prop-2E-enyl ester,

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]propyl ester,

N-Methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-(3-Methyl-but-1-yl)-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-

(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-*iso*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Cyclopentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-(R,S) *sec*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-*tert*-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-3,5-Dimethylcyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-*iso*-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

(S)-4-Methyl-2-([4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-benzoyl]-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-amino)-pentanoic acid ethyl ester,

N-Benzyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-

pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Propyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-propyl}-benzamide,

N-Cyclopropyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

(R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]but-3E-en-2-yl ester,

N-Cyclohexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-p-chlorophenyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-4-Tetrahydropyranyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Butyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Pentyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Nonyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Hexyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Methyl-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

(R,S)-4-(1H-2-Methylimidazo[4,5-c]pyridin-1-ylmethyl)benzoic acid (E)-1-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]hex-1E-en-3-yl ester,

N-Ethyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-3-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-propylamide,

N-Cyclohexyl-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-4-(1H-2-methylimidazo[4,5-c]pyridin-1-yl)-butylamide

N-Cyclohexyl-3-fluoro-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

N-Cyclohexyl-3-methoxy-4-(1H-2-methylimidazo[4,5-c]pyridin-1-ylmethyl)-N-{3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-1E-enyl)-pyridin-2-yl]-prop-2E-enyl}-benzamide,

and their pharmaceutically or vererinarily acceptable salts, hydrates and solvates.

19. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of the preceding claims together with a pharmaceutically or veterinarily acceptable carrier.

20. A composition as claimed in claim 19 which is adapted for oral administration.

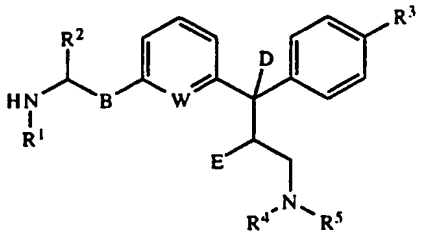
21. A method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF in mammals, including humans, which method comprises administering to the mammal an effective amount of a compound as as claimed in any one of claims 1 to 18.

22 A compound as as claimed in any one of claims 1 to 18 for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF.

23. The use of a compound as as claimed in any one of claims 1 to 18 in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF.

24. A method as claimed in claim 21, a compound for use as claimed in claim 22, or the use as claimed in claim 23, wherein the disease or condition referred to is hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, increased vascular permeability (oedema/erythema), allergic rhinitis, sinusitis, asthma, dermatitis, psoriasis, urticaria, anaphylactic shock, conjunctivitis, pruritis, inflammatory bowel disease or colitis.

25. An intermediate of formula (V), useful in the preparation of compounds of claim 1 wherein X represents -N(R^1)- ,



(V)

wherein R^1, R^2, B, W, D, E, R^3, R^4 and R^5 are as defined in claim 1.

26. An intermediate as claimed in claim 1 wherein R^1 is cyclohexyl, methyl or ethyl; R^2 is hydrogen; B is -CH=CH- (trans); R^3 is methyl; W is -N=; D and E taken together represent -C=C-; and R^4 and R^5 together represent a group $-(CH_2)_m-$ wherein m is 4.

27. An intermediate as claimed in claim 26 which is:

methyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine,

ethyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine, or

cyclohexyl-{3-(6-[3-pyrrolidino-1-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-prop-2E-enyl}-amine.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 96/01849

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/435 C07D213/36 //(C07D471/04,235:00, 221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 085 959 (WELLCOME) 17 August 1983 see claim 1; example 30	1,19
A	US,A,4 621 094 (FINDLAY ET AL.) 4 November 1986 see claims 1,23	1,19
A	WO,A,92 14734 (PFIZER) 3 September 1992 cited in the application see page 1, paragraph 1 - page 2, paragraph 1; claim 1	1,19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 1996	6.11.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/GB 96/01849

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21 and 24 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 96/01849

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

information on patent family members

Inte onal Application No
PCT/GB 96/01849

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		CZ-B- 280504	14-02-96
		DE-D- 69200304	08-09-94
		DE-T- 69200304	08-12-94
		EP-A- 0572425	08-12-93
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		ZA-A- 9201005	12-08-93

Form PCT/ISA/210 (patent family annex) (July 1992)